09/924,656 To overcome 25 June 1997.

```
=> search GABA analogs
         33159 GABA
        170139 ANALOGS
L8         249 GABA ANALOGS
               (GABA(W)ANALOGS)

=> search inflam?
L9       162369 INFLAM?

=> search l8 and l9
L10           9 L8 AND L9

=> dis l10 1- bib abs
YOU HAVE REQUESTED DATA FROM 9 ANSWERS - CONTINUE? Y/(N):y

L10  ANSWER 1 OF 9  CA  COPYRIGHT 2003 ACS on STN
AN   138:24958  CA
TI   Preparation of GABA analogs as prodrugs
IN   Gallop, Mark A.; Cundy, Kenneth C.; Zhou, Cindy X.; Yao, Fenmei; Xiang,
     Jia-Ning; Ollman, Ian R.; Qui, Fayang G.
PA   Xenoport, Inc., USA
SO   PCT Int. Appl., 148 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.         KIND  DATE          APPLICATION NO.  DATE
     ---------------    ----  --------      ---------------  --------
PI   WO 2002100347      A2    20021219      WO 2002-US18689  20020611
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
             CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     US 2003083382       A1    20030501      US 2002-170127   20020611
PRAI US 2001-297521P     P     20010611
     US 2001-298514P     P     20010614
     US 2002-366090P     P     20020319
OS   MARPAT 138:24958
AB   The invention provides prodrugs of GABA analogs and
     pharmaceutical compns. contg. these prodrugs for treating or preventing
     common diseases and/or disorders.  Compds. of formulas
     R1(X-CHR2CO)nNHCHR3CR4R5CHR6CO-Y-R7 [n = 0 or 1; X = O or an imino group;
     Y = O or S; R1 = (thio)acyl or phosphoryl groups, alkylthio, arylthio,
     etc.; R2-R7 = H, (cyclo)alkyl, aryl, etc.; CR4R5 = (un)substituted
     cyclo(hetero)alkyl, bridged cycloalkyl], R20R21C:(NCHR2CO)t(X-
     CHR2CO)uNHCHR3CR4R5CHR6CO-Y-R7 [t, u = 0 or 1; R20, R21 = groups similar
     to R4 and R5] , and R1(X-CHR2CO)nNRCHR3CR4R5CHR6CO-R [R2 = CR22R23O (to
     form a lactone), where R22, R23 are groups similar to R4 and R5] are
     claimed.  Thus, 1-[[[[(pivaloyloxy)methoxy]carbonyl]amino]methyl]-1-
     cyclohexaneacetic acid (51) was prepd. by acylation of gabapentin with
     p-nitrophenyl pivaloyloxymethyl carbonate (prepn. given).  In vitro Caco-2
     cellular permeabilities of the prodrugs were detd., with compd. 51 having
     Papp (apical to basolateral) and Papp (basolateral to apical) values of
     1.06x10-4 and 1.25x10-5 cm/s, resp.

L10  ANSWER 2 OF 9  CA  COPYRIGHT 2003 ACS on STN
AN   138:24957  CA
TI   Amino acid conjugates providing for sustained systemic concentrations of
     GABA analogs
IN   Gallop, Mark A.; Cundy, Kenneth C.; Scheuerman, Randall A.; Barrett,
     Ronald W.
PA   Xenoport, Inc., USA
SO   PCT Int. Appl., 111 pp.
```

CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 9

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002100344	A2	20021219	WO 2002-US18493	20020611

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-297732P P 20010611
US 2002-364619P P 20020318
OS MARPAT 138:24957
AB The invention is directed to compds. H-Ij-Jj-D-Kk-OH [D is a moiety derived from a GABA analog; I is -[NR50-(CR51R52)a-(CR53R54)b-CO]-; J is [NR55(CR56R57)c-(CR58R59)d-CO]-; K is -[NR60-(CR61R62)e-(CR63R64)f-CO]-; where a-f, i-k are 0 or 1, provided that at least one of a and b, c and d, e and f, and i-k is 1; R50-R64 = H, alkyl, (hetero)aryl, etc. or may combine to form a ring] that provide for sustained systemic concns. of **GABA analogs** following administration to animals. Thus, a series of aminoacyl-gabapentin derivs. and L-4-bromophenylalanine-pregabalin were prepd. and shown to elicit PEPT-specific currents significantly above background when tested at 1 mM on oocytes expressing either PEPT1 or PEPT2, thus confirming that these compds. serve as substrates for both of these transporters.

L10 ANSWER 3 OF 9 CA COPYRIGHT 2003 ACS on STN
AN 137:389160 CA
TI Liquid pharmaceutical composition containing **GABA analogs** and polyhydric alcohols
IN Kulkarni, Neema Mahesh; Schneider, Michael; Silbering, Steven Bernard; Meyer-wonnay, Hans Richard
PA Warner-Lambert Company, USA
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002094220	A1	20021128	WO 2002-IB1500	20020429

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002198261	A1	20021226	US 2002-156213	20020528

PRAI US 2001-293832P P 20010525
US 2001-343733P P 20011025
AB A liq. pharmaceutical compn. of a GABA analog comprising at least one polyhydric alc. contg. 2 to 6 carbon atoms having a pH of about 5.5 to about 7.0 and addnl. a two-component liq. pharmaceutical compn. comprising a first component comprising a powder mixt. comprising a GABA analog and a solid polyhydric alc., and a second component comprising a liq. base are described, as well as methods to prep. the compns. and a method for treating cerebral diseases, including epilepsy, faintness attacks, hypokinesia and cranial traumas, neurodegenerative disorders, depression,

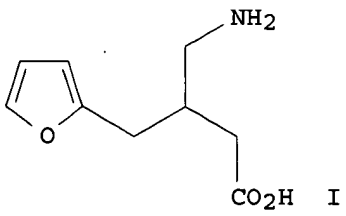
mania and bipolar disorders, anxiety, panic, **inflammation**, renal colic, insomnia, gastrointestinal damage, incontinence, pain, including neuropathic pain, muscular pain, skeletal pain, and migraine using a therapeutically effective amt. of the pharmaceutical compns. A liq. compn. contained gabapentin, xylitol, glycerol, flavors and water.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 9 CA COPYRIGHT 2003 ACS on STN
AN 134:29300 CA
TI Preparation of 3-heteroarylalkyl substituted **GABA analogs** as anticonvulsants
IN Yuen, Po-Wai
PA Warner-Lambert Company, USA
SO PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000073296	A2	20001207	WO 2000-US11397	20000428
WO 2000073296	A3	20010719		
W: AE, AG, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000011039	A	20020226	BR 2000-11039	20000428
EP 1185524	A2	20020313	EP 2000-928498	20000428
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003500486	T2	20030107	JP 2000-621362	20000428
PRAI US 1999-136491P	P	19990528		
WO 2000-US11397	W	20000428		

OS MARPAT 134:29300
GI



I

AB Title compds. [RCH2CH(CH2NH2)CH2COOH; R = thiophenyl, furanyl, pyrrolyl] are prepd. and are useful in the treatment of epilepsy, faintness attacks, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathol. disorders, gastrointestinal disorders such as irritable bowel syndrome (IBS), and **inflammation**, esp. arthritis. A pharmaceutical compn. contg. a compd. of title compd. as well as methods of prepg. the compds. and novel intermediates useful in the prepn. of the final compds. are included. Thus, the title compd. I was prepd. and tested in mice for prevention of audiogenic seizures.

L10 ANSWER 5 OF 9 CA COPYRIGHT 2003 ACS on STN
AN 133:344633 CA
TI Modulation of substance P by **GABA analogs**, and therapeutic methods
IN Magistro, Philip John, Jr.
PA Warner-Lambert Company, USA
SO PCT Int. Appl., 27 pp.

CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000067742	A2	20001116	WO 2000-US6199	20000310
WO 2000067742	A3	20010816		

W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-132614P P 19990505
OS MARPAT 133:344633
AB Modulation of substance P by **GABA analogs** is disclosed. Preferred GABA analog compds. include gabapentin and pregabalin. Methods of the invention include the modulation of substance P, as well as methods for preventing or treating conditions assocd. with substance P, by administering to an animal an effective amt. of one or more GABA analog compds. Conditions assocd. with substance P include headaches and migraine, neurogenic **inflammation**, emesis, nausea and vomiting, cough and bronchitis, obesity, allergy, asthma, hemorrhoids and anal fissures, ulcer, fever, infertility and periodontal disease.

L10 ANSWER 6 OF 9 CA COPYRIGHT 2003 ACS on STN
AN 132:102843 CA
TI **GABA analogs** for preventing and treating gastrointestinal damage
IN Guglietta, Antonio; Taylor, Charles Price, Jr.; Ren, Jiayuan; Watson, W. P.; Rafferty, Michael Francis; Diop, Laurent; Chovet, Maria; Bueno, Lionel; Little, Hilary J.
PA Jouveinal, Fr.
SO Eur. Pat. Appl., 20 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 974351	A2	20000126	EP 1998-401018	19980424
EP 974351	A3	20001213		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRAI EP 1998-401018 19980424
OS MARPAT 132:102843
AB **GABA analogs** are useful to prevent and treat gastrointestinal damage and ethanol withdrawal syndrome. Preferred treatments employ gabapentin or pregabalin.

L10 ANSWER 7 OF 9 CA COPYRIGHT 2003 ACS on STN
AN 130:191891 CA
TI **GABA analogs** to prevent and treat gastrointestinal damage and ethanol withdrawal syndrome
IN Guglietta, Antonio; Taylor, Charles, Price, Jr.; Ren, Jiayuan; Watson, W. P.; Rafferty, Michael Francis; Diop, Laurent; Chovet, Maria; Bueno, Lionel; Little, Hilary J.
PA Warner-Lambert Company, USA; The University of Oklahoma
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9908671	A1	19990225	WO 1998-US17082	19980818

W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL,

IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU	9892930	A1	19990308	AU 1998-92930	19980818
EP	1009399	A1	20000621	EP 1998-945758	19980818
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR	9812133	A	20000718	BR 1998-12133	19980818
JP	2001515033	T2	20010918	JP 2000-509411	19980818
CA	2297163	C	20011120	CA 1998-2297163	19980818
NZ	502729	A	20021025	NZ 1998-502729	19980818
ZA	9807493	A	19990707	ZA 1998-7493	19980819
US	6127418	A	20001003	US 1999-284710	19990419
MX	200001093	A	20001020	MX 2000-1093	20000131
NO	2000000786	A	20000217	NO 2000-786	20000217
US	6242488	B1	20010605	US 2000-567191	20000509
US	2001014698	A1	20010816	US 2001-804742	20010313
US	6426368	B2	20020730		
PRAI US	1997-56753P	P	19970820		
US	1998-74794P	P	19980216		
US	1998-82936P	P	19980424		
WO	1998-US17082	W	19980818		
US	1999-284710	A3	19990419		
US	2000-567191	A3	20000509		

OS MARPAT 130:191891

AB **GABA analogs** are useful to prevent and treat gastrointestinal damage and ethanol withdrawal syndrome. Preferred treatments employ gabapentin or pregabalin.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 9 CA COPYRIGHT 2003 ACS on STN

AN 130:191890 CA

TI **GABA analogs** to prevent and treat gastrointestinal damage and ethanol withdrawal syndrome

IN Guglietta, Antonio; Taylor, Charles Price, Jr.; Ren, Jiayuan; Watson, W. P.; Rafferty, Michael Francis; Diop, Laurent; Chovet, Maria; Bueno, Lionel; Little, Hilary J.

PA Warner-Lambert Company, USA; The University of Oklahoma; Taylor, Charles Price, Jr.; et al.

SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9908670	A1	19990225	WO 1998-US15694	19980729
W:	AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU	9886685	A1	19990308	AU 1998-86685	19980729
ZA	9807493	A	19990707	ZA 1998-7493	19980819
US	6242488	B1	20010605	US 2000-567191	20000509
PRAI US	1997-56753P	P	19970820		
US	1998-74794P	P	19980216		
US	1998-82936P	P	19980424		
WO	1998-US15694	W	19980424		
US	1999-284710	A3	19990419		

OS MARPAT 130:191890

AB **GABA analogs** are useful to prevent and treat gastrointestinal damage and ethanol withdrawal syndrome. Preferred

treatments employ gabapentin or pregabalin.
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 9 CA COPYRIGHT 2003 ACS on STN
AN 130:90504 CA
TI Use of **GABA analogs** such as gabapentin in the manufacture of a medicament for treating **inflammatory** diseases
IN Schrier, Denis; Taylor, Charles Price, Jr.; Westlund-High, Karin Nanette
PA Warner-Lambert Company, USA; Board of Regents of the University of Texas System
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9858641	A1	19981230	WO 1998-US13107	19980624
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	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9883758	A1	19990104	AU 1998-83758	19980624
	AU 735675	B2	20010712		
	ZA 9805517	A	19990120	ZA 1998-5517	19980624
	EP 994704	A1	20000426	EP 1998-934170	19980624
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	BR 9812265	A	20000718	BR 1998-12265	19980624
	JP 2002506449	T2	20020226	JP 1999-505021	19980624
	NZ 501626	A	20020328	NZ 1998-501626	19980624
	US 6329429	B1	20011211	US 1999-403867	19991025
	MX 9909996	A	20000331	MX 1999-9996	19991029
	NO 9906468	A	20000221	NO 1999-6468	19991223
	US 2002032235	A1	20020314	US 2001-924656	20010808
PRAI	US 1997-50736P	P	19970625		
	US 1998-84183P	P	19980504		
	WO 1998-US13107	W	19980624		
	US 1999-403867	A3	19991025		

OS MARPAT 130:90504
AB **GABA analogs**, e.g. gabapentin and pregabalin, are useful for the prevention and treatment of **inflammatory** diseases.
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>

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=> search GABA
L1       33159 GABA

=> search search inflam?
         65421 SEARCH
        162369 INFLAM?
L2           0 SEARCH INFLAM?
                 (SEARCH(W)INFLAM?)

=> search inflam?
L3      162369 INFLAM?

=> search l1 and l3
L4         210 L1 AND L3

=> search treat?
L5     2877429 TREAT?

=> search l4 and l5
L6          75 L4 AND L5

=> dis l6 1- bib abs
YOU HAVE REQUESTED DATA FROM 75 ANSWERS - CONTINUE? Y/(N):y

L6   ANSWER 1 OF 75  CA  COPYRIGHT 2003 ACS on STN
AN   139:133463  CA
TI   Heteroaryl substituted pyrrole modulators of metabotropic glutamate
     receptor-5
IN   Cosford, Nicholas D. P.; Smith, Nicholas D.; Huang, Dehua
PA   Merck & Co., Inc., USA
SO   PCT Int. Appl., 67 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
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PI   WO 2003059904      A1   20030724      WO 2002-US40486  20021217
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
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             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS,
             LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
             PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
             UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
             TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
             CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
PRAI US 2001-343262P   P    20011221
OS   MARPAT 139:133463
GI
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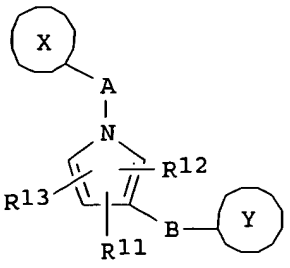

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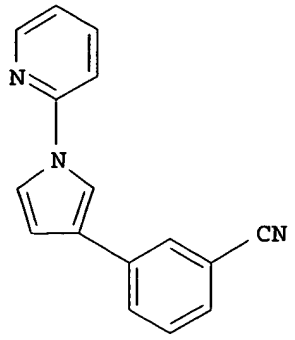


II

AB Title compds. I [X, Y = (hetero)aryl wherein at least one of X, Y is heteroaryl with N adjacent to the position of attachment; R11-13 = halo, alkyl, alkoxy, etc.] are prepd. For instance, 2-(3-bromo-1H-pyrrolyl)pyridine (prepn. given) is reacted with 3-cyanophenylboronic acid (DME, Pd(PPh3)4, K2CO3, 84.degree., 42 h) to give II. Example compds. have mGluR5 inhibitory activity with IC50 = 10 .mu.M or better. I are useful in the **treatment** of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, bipolar disorder and panic, as well as in the **treatment** of pain, circadian rhythm disorders, and other diseases.

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 139:112167 CA
TI Pregnane steroids for use in the **treatment** of steroid-related CNS disorders
IN Baeckstroem, Torbjoern; Lundgren, Per; Wang, Ming-de; Johansson, Inga-maj
PA Umecrine Ab, Swed.
SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003059357	A1	20030724	WO 2002-SE2423	20021220

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI SE 2001-4423 A 20011227
AB Steroid compds. possessing a hydrogen donor in 3.beta. position, either in the form of a hydroxy- or a sulfate group, function as efficient blockers of the 3.alpha.-hydroxy-pregnane-steroid action and thus have utility as therapeutic substances for the prevention and/or **treatment** of steroid related CNS disorders. **Treatment** methods based on the administration of these substances are disclosed, and these substances either alone or in combination are also suggested for the manuf. of pharmaceuticals for the **treatment** of many specific steroid induced CNS disorders.

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

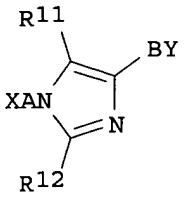
L6 ANSWER 3 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 139:85347 CA
TI Preparation of imidazolylpyridines as modulators of metabotropic glutamate

receptor subtype 5 (mGluR5).
IN Cosford, Nicholas D. P.; Smith, Nicholas D.; Huang, Dehua
PA Merck & Co., Inc., USA
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003053922	A2	20030703	WO 2002-US40237	20021216

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-341963P P 20011219
OS MARPAT 139:85347
GI



I

AB Title compds. [I; X, Y = (substituted) aryl, heteroaryl wherein .gtoreq.1 of X and Y = heteroaryl with N adjacent to the position of attachment to A or B; A = A1, A1SOA1, A1SO2A1, A1COA1, A1NR9COA1, A1NR9SO2A1, heteroalkyl; B = A1, A1SOA1, A1SO2A1, A1COA1, A1NR10COA1, A1NR10OSO2A1, heteroalkyl; R11, R12 = halo, O, (substituted) A1, alkoxy, NA1, N(A1)2; A1 = alkyl; R9, R10 = (substituted) A1, cycloalkyl, aryl, heteroaryl], were prepd. Thus, 2-(4-bromo-1H-imidazol-1-yl)pyridine (prepn. given), 3-chlorophenylboronic acid, Pd(PPh3)4, and K2CO3 were heated in DME/H2O at 80.degree. for 18 h. to give 2-[4-(3-chlorophenyl)-1H-imidazol-1-yl]pyridine. I showed mGluR5 inhibitory activity with IC50<10 .mu.M in the calcium flux assay.

L6 ANSWER 4 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 139:69267 CA
TI Preparation of 2-benzimidazolylamines as ORL1-receptor agonists for the **treatment** of pain and **inflammatory** diseases
IN Ito, Fumitaka
PA Pfizer Inc., USA
SO Eur. Pat. Appl., 33 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 1069124	A1	20010117	EP 2000-305981	20000714

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

US 6340681	B1	20020122	US 2000-606921	20000629
JP 2001048879	A2	20010220	JP 2000-209374	20000711
JP 3276111	B2	20020422		
JP 2001039974	A2	20010213	JP 2000-211264	20000712
BR 2000002796	A	20010403	BR 2000-2796	20000714

PRAI WO 1999-IB1290 W 19990716
OS MARPAT 139:69267
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R1, R2 = H, halo, OH, etc.; R3, R4 = H, halo-alkyl, substituted alkyl, i.e., OH, alkoxy, alkyl-S, etc.; R5 = pheny, substituted cycloalkyl, i.e., H, halo, OH, etc.;] and their pharmaceutically acceptable salts were prepd. For example, N-alkylation of N-methylpiperazine by chlorobenzimidazolyl II, e.g., prepd. from 1,3-dihydro-1-(4-piperidinyl)-2H-benzimidazol-2-one in 2-steps, afforded 2-benzimidazolylamine III in 15% yield. In selective affinity studies of opioid receptors, i.e., ORL1, .mu., .kappa. and .delta., some examples of compds. I exhibited good ORL1-receptor agonist activity. Compds. I are claimed useful as analgesics.
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 139:57897 CA
TI Novel pharmaceutical composition of interferon gamma or pirfenidone combined with molecular diagnostics for the improved **treatment** of interstitial lung diseases
IN Bevec, Dorian; Ziesche, Rolf
PA Mondobiotech SA, Switz.
SO PCT Int. Appl., 80 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003051388	A2	20030626	WO 2002-CH691	20021212

PI W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRAI EP 2001-130011 A 20011218
AB The present invention relates to a novel pharmaceutical compn. of compds. having the biol. activity of interferon gamma (IFN-.gamma.) or pirfenidone in combination with a diagnostic array of candidate polynucleotides for the improved **treatment** of all forms of interstitial lung diseases, in particular of idiopathic pulmonary fibrosis (IPF). This invention describes the combination of mol. diagnosis and clin. therapy as a novel medication principle for redn. of mortality and improvement of disease management in interstitial lung diseases.

L6 ANSWER 6 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 139:53017 CA
TI Preparation of heteroaryl substituted pyrazole modulators of metabotropic glutamate receptor-5
IN Cosford, Nicholas D. P.; Chen, Chixu; Eastman, Brian W.; Huang, Dehua; Munoz, Benito; Prasit, Petpiboon; Smith, Nicholas D.
PA Merck & Co., Inc., USA
SO PCT Int. Appl., 131 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003051833	A2	20030626	WO 2002-US40147	20021213

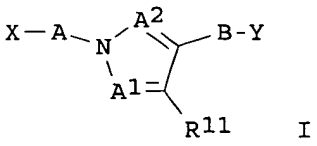
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-341382P P 20011218

OS MARPAT 139:53017

GI



I

AB Pyrazole compds. substituted directly, or by a bridge, with a heteroaryl moiety contg. N adjacent to the point of connection of the heteroaryl (shown as I; variables defined below; e.g. 3-[4-(pyridin-2-yl)-1H-pyrazol-1-yl]benzonitrile), are mGluR5 modulators useful in the **treatment** of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, bipolar disorder and panic, as well as in the **treatment** of pain, circadian rhythm disorders, and other diseases. Compds. I have mGluR5 inhibitory activity as shown by an IC50 value of <10 .mu.M and/or an inhibition of >30% at a concn. of 3 .mu.M in the Ca flux assay and/or inhibition of >50% at a concn. of 100 .mu.M in the phosphatidylinositol hydrolysis assay. For I: X and Y each independently is aryl or heteroaryl wherein at least one of X and Y is a heteroaryl with N adjacent to the position of attachment to A or B resp.; A is -C0-4-alkyl, -C0-2alkyl-SO-C0-2-alkyl-, -C0-2-alkyl-SO2-C0-2alkyl-, -C0-2-alkyl-CO-C0-2-alkyl-, -C0-2-alkyl-NR9CO-C0-2-alkyl-, -C0-2-alkyl-NR9SO2-C0-2-alkyl- or -heteroC0-4alkyl. B is -C0-4-alkyl, -C0-2-alkyl-SO-C0-2-alkyl-, -C0-2alkyl-SO2-C0-2alkyl-, -C0-2-alkyl-CO-C0-2-alkyl-, -C0-2-alkyl-NR10CO-C0-2-alkyl-, -C0-2-alkyl-NR10SO2-C0-2alkyl- or -heteroC0-4alkyl; one of A1 and A2 is N, the other is CR12; R11 and R12 is each independently halogen, -C0-6alkyl, -C0-6alkoxyl, or -N(C0-4-alkyl)(C0-4-alkyl), wherein optionally R11 and R12 are combined to form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring fused to the pyrazole moiety; any N may be an N-oxide; addnl. details including provisos are given in the claims. Although the methods of prepn. are not claimed, 15 example prepns. of I and 12 example prepns. of intermediates are included; characterization data are included for an addnl. .apprx.270 examples of I.

L6 ANSWER 7 OF 75 CA COPYRIGHT 2003 ACS on STN

AN 139:47469 CA

TI Differential regulation of GABAB receptor subunit expression and function

AU Sands, S. A.; McCarson, K. E.; Enna, S. J.

CS Department of Pharmacology, Toxicology and Therapeutics, Kansas University School of Medicine, Kansas City, KS, USA

SO Journal of Pharmacology and Experimental Therapeutics (2003), 305(1), 191-196
CODEN: JPETAB; ISSN: 0022-3565

PB American Society for Pharmacology and Experimental Therapeutics

DT Journal

LA English

AB The GABAB receptor is a G protein-coupled heterodimer composed of GABAB1 and GABAB2 subunits. In the present study, expts. were undertaken to examine the relationship between GABAB receptor function and subunit expression in the rat lumbar spinal cord following pharmacol. and physiol. manipulation of this receptor system. Although formalin-induced hind paw **inflammation** increases the prodn. of GABAB1 and GABAB2 protein in the spinal cord within 24 h, there is no change in receptor function, as measured by the baclofen-stimulated guanosine 5'-O-(3-[35S]thiotriphosphate) ([35S]GTP.gamma.S) binding assay. Conversely, although chronic (7 days) administration of baclofen, a GABAB receptor agonist, abolishes baclofen-stimulated [35S]GTP.gamma.S binding in the spinal cord tissue, causes tolerance to the sedative and antinociceptive effects of the drug, increases the no. of formalin-induced hind paw flinches, and induces mech. hyperalgesia, this **treatment** had no effect on the levels of GABAB1 or GABAB2 mRNAs in the lumbar spinal cord. The results indicate a lack of concordance between expression of GABAB1 and GABAB2 subunits and GABAB receptor function, suggesting these subunit proteins may serve multiple functions in the cells. Moreover, these findings indicate that nongenomic mechanisms are primarily responsible for the GABAB receptor desensitization that occurs during prolonged exposure to receptor agonist.

RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

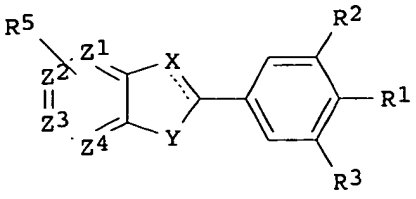
L6 ANSWER 8 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 139:36519 CA
TI Preparation of 2-phenylbenzoxazoles as metabotropic glutamate receptor-5 modulators for **treatment** of pain and CNS disorders
IN Munoz, Benito; Stearns, Brian; Vernier, Jean-Michel; Wang, Bowei; Bonnefous, Celine; Zhao, Xiumin; Arruda, Jeannie; Campbell, Brian T.; Cube, Rowena V.
PA Merck & Co., Inc., USA
SO PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003048137	A1	20030612	WO 2002-US38201	20021126

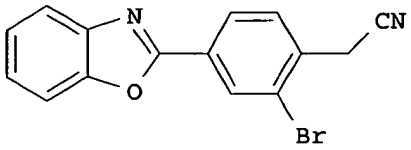
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-334547P P 20011130
OS MARPAT 139:36519
GI



I



II

AB Title compds. I [wherein X = N, CH, or NH; Y = O or NR4; Z1-Z4 = CH or 1 of Z1-Z4 = optionally N or NH; R1 = OH, halo, CN, or (un)substituted (cyclo)alkyl, alkoxy, alkylphenyl, alkylpyridyl, alkylimidazolyl, alkylpyrazolyl, alkyltriazolyl, alkyltetrazolyl, alkyldioxolanyl, alkylthiazolyl, alkylpiperidinyl, alkylpyrrolidinyl, alkylmorpholinyl, alkylpyrimidinyl, alkynylthiazolyl, or (di)alkylamino; R2 = H, halo, OH, CN, (di)alkylamino, NO2, or (un)substituted alkyl, alkoxy, alkylphenyl, or alkoxyphenyl; R3 = H or alkoxy; R4 = alkyl; R5 = H, halo, or alkyl; and pharmaceutically acceptable salts thereof] were prepd. as metabotropic glutamate receptor-5 (mGluR5) modulators. For example, amidation of 3-bromo-4-methylbenzoic acid with 2-aminophenol, followed by reflux with p-TsOH in toluene for 4 h gave 2-(3-bromo-4-methylphenyl)-1,3-benzoxazole. Bromination and substitution with NaCN in DMF/H2O afforded [4-(1,3-benzoxazol-2-yl)-2-bromophenyl]acetonitrile (II). Eighty compds. of the invention were tested in calcium flux and phosphatidylinositol hydrolysis assays and showed mGluR5 inhibitory activity with IC50 values of < 5 .mu.M and < 100 .mu.M, resp. Thus, I and pharmaceutical compns. comprising I are useful in the **treatment** of psychiatric and mood disorders, such as schizophrenia, anxiety, depression, and panic, as well as in the **treatment** of pain and other CNS diseases (no data).

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 9 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 139:31192 CA
TI Neurokinin 1 receptors and neprilysin modulation of mouse bladder gene regulation
AU Dozmorov, Igor; Saban, Marcia R.; Gerard, Norma P.; Lu, Bao; Nguyen, Ngoc-Bich; Centola, Michael; Saban, Ricardo
CS Oklahoma Medical Research Foundation, Microarray Research Facility, Univ. of Oklahoma Health Sciences Center, Oklahoma City, OK, 73104, USA
SO Physiological Genomics (2003), 12(3), 239-250
CODEN: PHGEFP; ISSN: 1094-8341
URL: http://physiolgenomics.physiology.org/cgi/reprint/12/3/239.pdf
PB American Physiological Society
DT Journal; (online computer file)
LA English
AB Neurokinin 1 (NK1) receptors play a fundamental role in neurogenic **inflammation**. the authors sought to det. the mechanisms downstream from NK1 receptor (NK1R)activation using cDNA arrays and a novel statistical method to analyze gene expression. The authors used female NK1R-/- and wild-type (WT) mice that were sensitized actively by i.p. injections of dinitrophenol 4 (DNP4)-human serum albumin. Cystitis was induced by intravesical instillation of antigen of DNP4-ovalbumin, and control mice were challenged with saline. At 1, 4, and 24 h after instillation,bladders were removed for RNA extn. (n = 3), replicate of RNA extn. (n = 3), and morphol. anal. (n = 6). For cDNA array expts., three bladders from each group were homogenized, and total RNA was obtained. DNase-**treated** RNA was reverse-transcribed to cDNA, labeled with [.alpha.-32P]dATP and hybridized to Atlas Mouse 1.2 Arrays. After calcg. the mean and SD for background spots, each exptl. value was assigned a normalized score S using the formula S' = (S - Av)/SD, where S' is the

original pixel value, and Av and SD are the mean and std. deviation of background spots, resp. Only genes that expressed 3 SD values above background were used. Hypervariable genes were sorted by cluster anal. Matrixes of correlation coeffs. were calcd. and represented in a connectivity mosaic. As results, the authors found that in WT mice the most prominent gene cluster had neprilysin in a central position and pos. correlated to a group of activator protein-1 (AP-1)-responsive genes, including laminin-.alpha.3, tissue plasminogen activator 11, fos-B, and TNF-.beta.. In WT mice, antigen-induced bladder **inflammation** led to a downregulation in neprilysin expression. In contrast, NK1R-/- mice failed to mount an **inflammatory** reaction and presented neprilysin neg. correlated with the same genes described in WT. In conclusion, this work indicates an overriding participation of NK1R and neprilysin in bladder **inflammation**, provides a working model for the involvement of AP-1 transcription factor, and evokes testable hypotheses regarding the role of NK1R and neprilysin in **inflammation**.

RE.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 139:932 CA
TI Use of **GABA** for the **treatment** of intestinal **inflammation**
IN Kalousek, Markus B.; Grimmecke, Hans-Dieter; Seibold, Frank
PA Laves Arzneimittel G.m.b.H., Germany
SO PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

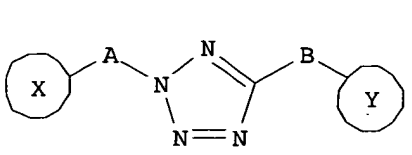
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003045360	A2	20030605	WO 2002-EP12001	20021028
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10158601	A1	20030612	DE 2001-10158601	20011129
PRAI DE 2001-10158601	A	20011129		

AB The invention discloses the use of **GABA** (prepn. included) for **treating** intestinal **inflammation** which is not mediated by T cells.

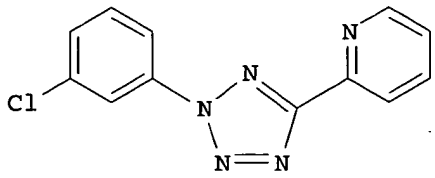
L6 ANSWER 11 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 138:287681 CA
TI Preparation of heteroaryl substituted tetrazole modulators of metabotropic glutamate receptor-5
IN Cosford, Nicholas D.; Roppe, Jeffrey; Chen, Chixu; Smith, Nicholas; Reger, Thomas
PA Merck & Co. Inc., USA
SO PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003029210	A2	20030410	WO 2002-US31294	20021001
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS,				

LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG
PRAI US 2001-327132P P 20011004
OS MARPAT 138:287681
GI



I



II

AB Title compds. I [X, Y = (un)substituted (hetero)aryl; A, B = alkyl, alkyl-SO-alkyl, alkyl-SO2-alkyl, etc.] are prepd. For instance, 2-formylpyridine is condensed with toluenesulfonyl hydrazide to form the hydrazone. 3-Chloroaniline is converted to the diazonium salt and reacted with the hydrazone to form 2-[2-(3-chlorophenyl)-2H-tetrazol-5-yl]pyridine (II) as a pale orange solid. Compds. of the invention have IC50 < 10.mu.M for mGluR5 in the calcium flux assay. I are mGluR5 modulators useful in the **treatment** of psychiatric and mood disorders such as, schizophrenia, anxiety, depression, and panic, as well as in the **treatment** of pain and other diseases.

L6 ANSWER 12 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 138:260460 CA
TI Pharmaceutical composition for brain and spinal cord injuries
IN Wang, Yanming
PA USA
SO U.S. Pat. Appl. Publ., 9 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2003059476	A1	20030327	US 2001-962009	20010924
WO 2003026565	A2	20030403	WO 2002-US28918	20020911

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-962009 A 20010924
AB After interruption of blood supply to central nervous system tissue, cerebral edema sets in. It has been shown that restoring blood flow to injured areas of the central nervous system after the onset of edema does not result in blood reperfusing the tissue. A compn. and method for **treating** injured central nervous tissue, or preventing injury to central nervous system tissue is provided. The compn. is generally an amphipathic lipid in an oil soln. The method provides for withdrawing cerebrospinal fluid from the subarachnoid spaces around the tissue to be **treated** or protected, and replacing that fluid with an approx.

equiv. vol. of the amphipathic lipid in oil compn. The **treatment** can be augmented with agents that suppress prodn. of cerebrospinal fluid, or with other known agents. Acute spinal cord ischemia was induced in 29 rabbits. At both 24 h and 1 wk after ischemia, in group 1 (soybean oil **treatment**) and group 2 [vitamin E injection soln. (1 mg/mL)] **treatment** all rabbits showed no behavioral deficit, all walked and moved smoothly. In group 3 (12 rabbits for control), all of rabbits showed complete spastic paraplegia with no movement to the hind limbs.

L6 ANSWER 13 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 138:249938 CA
TI Gene expression profile biomarkers and therapeutic targets for brain aging and age-related cognitive impairment in rats
IN Landfield, Philip W.; Blalock, Eric M.; Chen, Kuey-Chu; Foster, Thomas C.
PA University of Kentucky Research Foundation, USA
SO PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003025122	A2	20030327	WO 2002-US25607	20020813

PI
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-311343P P 20010813
AB A statistical and functional correlation strategy is provided to identify changes in cellular pathways specifically linked to impaired cognitive function with aging. Analyses using the strategy identified multiple groups of genes expressed in the hippocampal CA1 region of rats, where the genes were expressed at different levels for several ages. The aging changes in expression began before mid-life. Many of the genes were involved in specific neuronal and glial pathways with previously unrecognized relationships to aging and/or cognitive decline. The processes identified by the strategy suggest a new hypothesis of brain aging in which initially decreased neuronal activity and/or oxidative metab. trigger sep. but parallel genomic cascades in neurons and glia. In neurons, the cascade results in elevations in calcium signaling and redns. of immediate early gene signaling, biosynthesis, synaptogenesis, and neurite remodeling. In contrast, glia undergo increased lipid metab. and mediate a cycle of demyelination and remyelination that induces antigen presentation, **inflammation**, oxidative stress, and extracellular restructuring. These identified genes and the proteins they encode can be used as novel biomarkers of brain aging and as targets for developing **treatment** methods against age-related cognitive decline, Alzheimer's disease, and Parkinson's disease.

L6 ANSWER 14 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 138:105388 CA
TI IL-4 increases GABAergic phenotype in rat retinal cell cultures: involvement of muscarinic receptors and protein kinase C
AU Sholl-Franco, Alfred; Marques, Patricia M. B.; Ferreira, Cecilia M. C.; de Araujo, Elizabeth G.
CS Centro de Estudos Gerais, Instituto de Biologia, Programa de Neuroimunologia, Departamento de Neurobiologia, Universidade Federal Fluminense, Niteroi, RJ, 24001-970, Brazil
SO Journal of Neuroimmunology (2002), 133(1-2), 20-29
CODEN: JNRIDW; ISSN: 0165-5728
PB Elsevier Science B.V.
DT Journal

LA English
AB Interleukin-4 (IL-4) is an anti-**inflammatory** cytokine. During injuries, infections, and neurodegenerative diseases, high levels of this mol. are expressed in the brain. Here, the authors investigated the effect of IL-4 on GABAergic differentiation of retinal cells kept in vitro. They analyzed either the uptake of [3H]-.gamma.-aminobutyric acid (**GABA**) or the expression of glutamic acid decarboxylase (GAD-67) following IL-4 **treatment**. They also investigated the pharmacol. modulation of the [3H]-**GABA** uptake by cholinergic activation. The results demonstrate that IL-4 increases the uptake of [3H]-**GABA** after 48 h in culture in a dose-dependent manner (0.5-100 U/mL). The maximal effect was obtained with 5 U/mL (75% increase). This effect was blocked by 1 mM of nipecotic acid, demonstrating the involvement of the GAT-1 subtype of **GABA** transporter. The IL-4 effect depends on M1 muscarinic activity, an increase in intracellular calcium levels, tyrosine kinase activity, and protein kinase C (PKC) activity. **Treatment** with IL-4 for 48 h induced an increase of 90% in the no. of GAD- and **GABA**-immunoreactive cells when compared with control cultures. Thus, IL-4 modulates the GABAergic phenotype of retinal cells in culture. This result can suggest an important role for this cytokine either during the normal development of retinal circuitry or during neuroprotection after injuries.
RE.CNT 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 15 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 138:32683 CA
TI Non-cholinergic strategies for **treating** and preventing Alzheimer's disease
AU Doraiswamy, P. Murali
CS Departments of Psychiatry and Medicine, Duke University Medical Center, Durham, NC, USA
SO CNS Drugs (2002), 16(12), 811-824
CODEN: CNDREF; ISSN: 1172-7047
PB Adis International Ltd.
DT Journal; General Review
LA English
AB A review. The pathophysiol. of Alzheimer's disease is complex and involves several different biochem. pathways. These include defective .beta.-amyloid (A.beta.) protein metab., abnormalities of glutamatergic, adrenergic, serotonergic and dopaminergic neurotransmission, and the potential involvement of **inflammatory**, oxidative and hormonal pathways. Consequently, these pathways are all potential targets for Alzheimer's disease **treatment** and prevention strategies. Currently, the mainstay **treatments** for Alzheimer's disease are the cholinesterase inhibitors, which increase the availability of acetylcholine at cholinergic synapses. Since the cholinesterase inhibitors confer only modest benefits, addnl. non-cholinergic Alzheimer's disease therapies are urgently needed. Several non-cholinergic agents are currently under development for the **treatment** and/or prevention of Alzheimer's disease. These include anti-amyloid strategies (e.g. immunization, aggregation inhibitors, secretase inhibitors), transition metal chelators (e.g. clioquinol), growth factors, hormones (e.g. estradiol), herbs (e.g. Ginkgo biloba), nonsteroidal anti-**inflammatory** drugs (NSAIDs, e.g. indomethacin), antioxidants, lipid-lowering agents, antihypertensives, selective phosphodiesterase inhibitors, vitamins (E, B 12, B6, folic acid) and agents that target neurotransmitter or neuropeptide alterations. Neurotransmitter receptor-based approaches include agents that modulate certain, receptors (e.g. nicotinic, muscarinic, .alpha.-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid [AMPA], .gamma.-aminobutyric acid [**GABA**], N-methyl-D-aspartate [NMDA]) and agents that increase the availability of neurotransmitters (e.g. noradrenergic reuptake inhibitors). Of these strategies, the NMDA receptor antagonist memantine is in the most advanced stage of development in the US and is already approved in Europe as the first **treatment** for moderately severe to severe Alzheimer's disease. Memantine is proposed to counteract cellular damage due to pathol. activation of NMDA receptors by glutamate. Results with Ginkgo biloba have been mixed. Data for neurotrophic therapies and vitamin E

(tocopherol) appear promising but require confirmation. NSAIDs and conjugated estrogens have not proven to be of value to date for the **treatment** of Alzheimer's disease. Statins may have a potential role in reducing the risk or delaying the onset of Alzheimer's disease, although this has yet to be confirmed in randomized trials. There are currently no data to support the use of statins as a **treatment** for dementia. This article provides an update on the current status of selected agents, focusing primarily on those agents with the most extensive clin. evidence at present.

RE.CNT 115 THERE ARE 115 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 16 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 138:24958 CA
TI Preparation of **GABA** analogs as prodrugs
IN Gallop, Mark A.; Cundy, Kenneth C.; Zhou, Cindy X.; Yao, Fenmei; Xiang, Jia-Ning; Ollman, Ian R.; Qui, Fayang G.
PA Xenoport, Inc., USA
SO PCT Int. Appl., 148 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002100347	A2	20021219	WO 2002-US18689	20020611
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2003083382	A1	20030501	US 2002-170127	20020611
PRAI	US 2001-297521P	P	20010611		
	US 2001-298514P	P	20010614		
	US 2002-366090P	P	20020319		

OS MARPAT 138:24958
AB The invention provides prodrugs of **GABA** analogs and pharmaceutical compns. contg. these prodrugs for **treating** or preventing common diseases and/or disorders. Compds. of formulas R1(X-CHR2CO)nNHCHR3CR4R5CHR6CO-Y-R7 [n = 0 or 1; X = O or an imino group; Y = O or S; R1 = (thio)acyl or phosphoryl groups, alkylthio, arylthio, etc.; R2-R7 = H, (cyclo)alkyl, aryl, etc.; CR4R5 = (un)substituted cyclo(hetero)alkyl, bridged cycloalkyl], R20R21C:(NCHR2CO)t(X-CHR2CO)uNHCHR3CR4R5CHR6CO-Y-R7 [t, u = 0 or 1; R20, R21 = groups similar to R4 and R5] , and R1(X-CHR2CO)nNRCHR3CR4R5CHR6CO-R [R2 = CR22R23O (to form a lactone), where R22, R23 are groups similar to R4 and R5] are claimed. Thus, 1-[[[[(pivaloyloxy)methoxy]carbonyl]amino]methyl]-1-cyclohexaneacetic acid (51) was prepd. by acylation of gabapentin with p-nitrophenyl pivaloyloxymethyl carbonate (prepn. given). In vitro Caco-2 cellular permeabilities of the prodrugs were detd., with compd. 51 having Papp (apical to basolateral) and Papp (basolateral to apical) values of 1.06x10-4 and 1.25x10-5 cm/s, resp.

L6 ANSWER 17 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 137:389160 CA
TI Liquid pharmaceutical composition containing **GABA** analogs and polyhydric alcohols
IN Kulkarni, Neema Mahesh; Schneider, Michael; Silbering, Steven Bernard; Meyer-wonnay, Hans Richard
PA Warner-Lambert Company, USA
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002094220	A1	20021128	WO 2002-IB1500	20020429
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2002198261	A1	20021226	US 2002-156213	20020528
PRAI	US 2001-293832P	P	20010525		
	US 2001-343733P	P	20011025		

AB A liq. pharmaceutical compn. of a **GABA** analog comprising at least one polyhydric alc. contg. 2 to 6 carbon atoms having a pH of about 5.5 to about 7.0 and addnl. a two-component liq. pharmaceutical compn. comprising a first component comprising a powder mixt. comprising a **GABA** analog and a solid polyhydric alc., and a second component comprising a liq. base are described, as well as methods to prep. the compns. and a method for **treating** cerebral diseases, including epilepsy, faintness attacks, hypokinesia and cranial traumas, neurodegenerative disorders, depression, mania and bipolar disorders, anxiety, panic, **inflammation**, renal colic, insomnia, gastrointestinal damage, incontinence, pain, including neuropathic pain, muscular pain, skeletal pain, and migraine using a therapeutically effective amt. of the pharmaceutical compns. A liq. compn. contained gabapentin, xylitol, glycerol, flavors and water.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 18 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 137:363504 CA
TI Increased synaptosomal [3H]**GABA** uptake in the rat brainstem after facial carrageenan injections
AU Ng, Chee-Hon; Ong, Wei-Yi
CS Department of Anatomy, National University of Singapore, Singapore, 119260, Singapore
SO Pain (2002), 98(3), 259-268
CODEN: PAINDB; ISSN: 0304-3959
PB Elsevier Science B.V.
DT Journal
LA English
AB The aim of the present study was to quantify synaptosomal [3H] gamma aminobutyric acid (**GABA**) uptake in the rat brainstem after facial carrageenan injections. Synaptosomal prepns. from the brainstem of rats that had received one or four facial carrageenan injections showed greater **GABA** binding on the side of the brainstem ipsilateral to the carrageenan injection than on the contralateral side when compared to saline injected controls. In contrast, no difference in **GABA** binding between the injected and contralateral sides was obsd. in the same synaptosomal prepns. that had been **treated** with **GABA** uptake inhibitors NNC-711, .beta.-alanine, or nipecotic acid. The difference between **GABA** binding in the absence of the **GABA** uptake inhibitor and **GABA** binding in a portion from the same synaptosomal prepn. which had been incubated with the **GABA** uptake inhibitor was obtained to represent [3H]**GABA** binding to **GABA** transporters/transporter mediated [3H] **GABA** uptake. A significantly greater **GABA** uptake was obsd. on the side of the brainstem ipsilateral to the carrageenan injection(s) than on the contralateral side. A consequence of the obsd. increase in **GABA** uptake is that it could reduce the amt. of **GABA** in the synaptic cleft. This could influence the transmission of nociceptive input from primary afferents to secondary neurons in the spinal trigeminal nucleus and could be a contributing factor in the development of hyperalgesia after carrageenan injections or other chronic **inflammatory** conditions.

RE.CNT 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 19 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 137:92002 CA
TI DNA microarray analysis of the contused spinal cord: Effect of NMDA receptor inhibition
AU Nesic, O.; Svrakic, N. M.; Xu, G-Y.; McAdoo, D.; Westlund, K. N.; Hulsebosch, C. E.; Ye, Zeiming; Galante, A.; Soteropoulos, P.; Tolias, P.; Young, W.; Hart, R. P.; Perez-Polo, J. R.
CS Department of Human Biological Chemistry and Genetics, University of Texas Medical Branch, Galveston, TX, USA
SO Journal of Neuroscience Research (2002), 68(4), 406-423
CODEN: JNREDK; ISSN: 0360-4012
PB Wiley-Liss, Inc.
DT Journal
LA English
AB Spinal cord injury (SCI)-induced neurodegeneration leads to irreversible and devastating motor and sensory dysfunction. Post-traumatic outcomes are detd. by events occurring during the first 24 h after SCI. An increase in extracellular glutamate concn. to neurotoxic levels is one of the earliest events after SCI. We used Affymetrix DNA oligonucleotide microarrays (with 1322 DNA probes) anal. to measure gene expression in order to test the hypothesis that SCI-induced N-methyl-D-aspartate (NMDA) receptor activation triggers significant postinjury transcriptional changes. Here we report that SCI, 1 h after trauma, induced change in mRNA levels of 165 genes and expression sequence tags (ESTs). SCI affected mRNA levels of those genes that regulate predominantly transcription factors, **inflammation**, cell survival, and membrane excitability. We also report that NMDA receptor inhibition (with -(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5, 10-imine hydrogen maleate [MK-801]) reversed the effect of SCI on about 50% of the SCI-affected mRNAs. Esp. interesting is the finding that NMDA receptor activation participates in the up-regulation of **inflammatory** factors. Therefore, SCI-induced NMDA receptor activation is one of the dominant, early signals after trauma that leads to changes in mRNA levels of a no. of genes relevant to recovery processes. The majority of MK-801 effects on the SCI-induced mRNA changes reported here are novel. Addnl., we found that the MK-801 **treatment** also changed the mRNA levels of 168 genes and ESTs that had not been affected by SCI alone, and that some of their gene products could have harmful effects on SCI outcome.
RE.CNT 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 20 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 137:88615 CA
TI Age-Dependent Changes in 24-Hour Rhythms of Thymic and Circulating Growth Hormone and Adrenocorticotropin in Rats Injected with Freund's Adjuvant
AU Esquifino, Ana I.; Bonacho, Manuel Garcia; Arce, Agustin; Cutrera, Rodolfo A.; Cardinali, Daniel P.
CS Departamento de Bioquimica y Biologia Molecular III, Universidad Complutense, Facultad de Medicina, Madrid, Spain
SO NeuroImmunoModulation (2002), Volume Date 2001, 9(5), 237-246
CODEN: NROIEM; ISSN: 1021-7401
PB S. Karger AG
DT Journal
LA English
AB Objective: To analyze the 24-h changes in thymic and serum concn. of growth hormone (GH) and ACTH and their correlation with thymic concns. of glutamate, aspartate, taurine and **GABA** in young and old rats during the acute phase of adjuvant's arthritis. Methods: Young (50-day-old) and old (18-mo-old) rats were injected s.c. with Freund's adjuvant or its vehicle (paraffin oil contg. 15% mannide monooleate). Eighteen days later, they were killed at six different time intervals throughout a 24-h cycle. Serum and thymic levels of GH and ACTH were measured by RIA. Thymic amino acid concn. was measured by HPLC. A quant. assessment of arthritis was made in an independent group of rats by plethysmog. Results: Old rats injected with Freund's adjuvant exhibited fewer clin. signs of **inflammation** than young rats. Significant

24-h changes in thymic and serum GH occurred, except for serum GH in adjuvant's vehicle-**treated** old rats. Aging augmented thymic GH and decreased serum GH. Immunization with Freund's adjuvant did not modify GH concn. Thymic and serum concn. of GH correlated neg. Thymic ACTH varied significantly over 24 h with maxima during the dark phase, except in Freund's adjuvant-**treated** young rats. Maximal serum ACTH levels occurred in the late afternoon except in Freund's adjuvant-**treated** old rats which showed maxima at night. Immunization with Freund's adjuvant augmented thymic and circulating concns. of ACTH. Thymic and serum concn. of ACTH correlated pos. Thymic concn. of glutamate, aspartate and taurine decreased in aged rats and correlated significantly with thymic ACTH. Conclusion: The results support the existence of a thymic compartment of GH and ACTH that may be independently regulated.

RE.CNT 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 21 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 136:335237 CA
TI Pharmaceutical combinations
IN Brearley, Christopher John; Butler, Paul; Chahwala, Suresh Babubhai; Chopp, Michael; Krams, Michael; Looby, Michael; MacIntyre, Fion; McElroy, Andrew Brian; McHarg, Aileen Dorothy
PA Pfizer Limited, UK; Pfizer Inc.
SO PCT Int. Appl., 110 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002032446	A2	20020425	WO 2001-IB1936	20011015
	WO 2002032446	A3	20020711		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2002098179	A1	20020725	US 2001-969271	20011001
PRAI	GB 2000-25473	A	20001017		
	US 2000-253847P	P	20001129		

AB This invention relates, inter alia, to methods of **treating** pathophysiol. conditions involving neutrophils, comprising administering to a patient in need of such **treatment** a combination therapy comprising at least one Neutrophil Inhibitory Factor (NIF) and at least one other agent that protects neurons from toxic insult, inhibits the **inflammatory** reaction after brain damage or promotes cerebral reperfusion (i.e. neuroprotective or thrombolytic/fribrinolytic agents), or a pharmaceutically acceptable salt thereof.

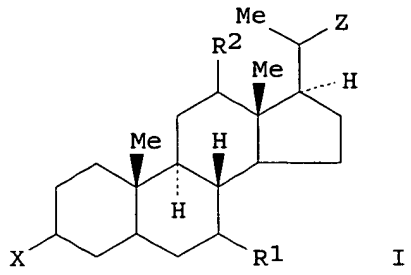
L6 ANSWER 22 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 136:310071 CA
TI Preparation of bile-acid derived compounds for sustained release of orally delivered drugs
IN Gallop, Mark A.; Cundy, Kenneth C.; Zhou, Cindy X.
PA Xenoport, Inc., USA
SO PCT Int. Appl., 214 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 9

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002028881	A1	20020411	WO 2001-US42513	20011005
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				

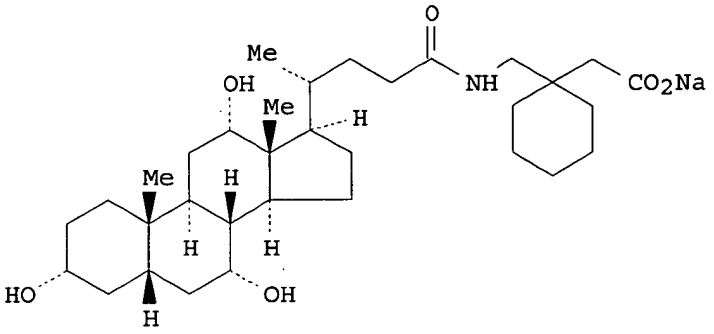
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU	2002011863	A5	20020415	AU 2002-11863	20011005
US	2002151529	A1	20021017	US 2001-972425	20011005
PRAI US	2000-238758P	P	20001006		
US	2000-249804P	P	20001117		
US	2001-297594P	P	20010611		
WO	2001-US42513	W	20011005		

OS MARPAT 136:310071
GI



I



II

AB Bile-acid conjugates such as I [R1, R2 = H, OH; X = OH, DQT; T = O, NH; Q = bond, cleavable linker; D = **GABA** analog; Z = alkyl substituted with CO2H, SO3H, SO2H, P(O)(OR6)(OH), OSO3H; R6 = (un)substituted alkyl, aryl, MQ'D'; M = CH2OC(O), CH2CH2C(O); Q' = bond, cleavable linker; D' = D], or their pharmaceutically acceptable salts, were prepd. for their use as substrates for an intestinal bile acid transporter, and thus I could be utilized to provides sustained systemic concns. of orally delivered drugs to an animal. Thus, prodrug II was prepd. via **treatment** of the acid with NaOH obtained by the reaction of cholic acid and 1-aminomethyl-1-cyclohexaneacetic acid hydrochloride. Prodrug II was pharmacol. tested [IC50 = 36 .mu.M vs. IBAT-expressing cells; IC50 = 8 .mu.M vs. LBAT-expressing cells].

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 23 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 136:96480 CA
TI Spinal GABAB-receptor antagonism increases nociceptive transmission in vivo
AU Sokal, David M.; Chapman, Victoria
CS School of Biomedical Sciences, E Floor, Medical School, University of Nottingham, Nottingham, NG7 2UH, UK
SO NeuroReport (2001), 12(15), 3247-3250
CODEN: NERPEZ; ISSN: 0959-4965

PB Lippincott Williams & Wilkins
DT Journal
LA English
AB GABAB receptors modulate primary afferent fiber evoked responses of spinal neurons. Here effects of the selective GABAB receptor antagonist, CGP-35348, on elec.-evoked responses of spinal neurons in control and carrageenan-**inflamed** rats were studied. Spinal CGP-35348 (0.1-10 .mu.g/50 .mu.l) did not alter A.beta.- or A.delta.-fiber evoked neuronal responses in control rats, although C-fiber evoked responses and post discharge responses of spinal neurons were significantly facilitated by 3.0 and 10.0 .mu.g/50 .mu.l CGP-35348. In carrageenan-**treated** animals, spinal CGP-35348 did not alter elec. evoked responses of spinal neurons at any dose. The authors' data suggest that following acute peripheral **inflammation** there is loss of endogenous GABAB receptor mediated inhibition of C-fiber transmission at the level of the spinal cord.
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 24 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 135:327259 CA
TI Involvement of GABAergic systems in manifestation of pharmacological activity of desipramine
AU Asahi, Yoshinao; Yonehara, Norifumi
CS Bobath Memorial Hospital, Osaka, 536-0023, Japan
SO Japanese Journal of Pharmacology (2001), 86(3), 316-322
CODEN: JJPAAZ; ISSN: 0021-5198
PB Japanese Pharmacological Society
DT Journal
LA English
AB We have conducted this study to elucidate the influence of GABAergic systems on manifestation of pharmacol. activity of desipramine using both pharmacol. and electrophysiol. methods. Desipramine (20 mg/kg, i.p.) significantly blocked the adjuvant-induced thermal hyperalgesia, which was facilitated by **treatment** with the GABAA antagonist picrotoxin (2 mg/kg, i.p.) or the GABAB antagonist saclofen (2 mg/kg, i.p.). This analgesic effect of desipramine was antagonized by post-**treatment** with picrotoxin or saclofen. However, none of these compds. showed any effect in normal animals without adjuvant-induced **inflammation**. In a slice prepn. of the hippocampus, **treatment** with **GABA** (10-5 - 5.times.10-4 M), baclofen (10-5 - 10-4 M) or muscimol (10-5 - 10-4 M) inhibited the field potential evoked in pyramidal neurons by Schaffer collateral stimulation. The inhibitory effect of **GABA** was facilitated by concurrent application of desipramine, carbamazepine or diazepam at a concn. of 5.times.10-5 - 2.times.10-4 M. The rank of order of facilitation is: desipramine > carbamazepine > diazepam. Desipramine also enhanced the inhibitory effect of baclofen and muscimol. These results suggest that desipramine causes GABAergic systems to activate still more, and this phenomenon appears to be involved in manifestation of the pharmacol. activity of desipramine such as antinociception.
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 25 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 135:225196 CA
TI Gene expression analysis in N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mice model of Parkinson's disease using cDNA microarray: effect of R-apomorphine
AU Grunblatt, Edna; Mandel, Silvia; Maor, Gila; Youdim, Moussa B. H.
CS Technion Faculty of Medicine, Bruce Rappaport Family Research Institute, Department of Pharmacology, Eve Topf and US National Parkinson's Foundation Centers for Neurodegenerative Diseases, Haifa, Israel
SO Journal of Neurochemistry (2001), 78(1), 1-12
CODEN: JONRA9; ISSN: 0022-3042
PB Blackwell Science Ltd.
DT Journal
LA English
AB To establish the possible roles of oxidative stress, **inflammatory** processes and other unknown mechanisms in neurodegeneration, we

investigated brain gene alterations in N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mice model of Parkinson's disease using Atlas mouse cDNA expression array membrane. The expression of 51 different genes involved in oxidative stress, **inflammation**, glutamate and neurotrophic factors pathways as well as in still undefined processes, such as cell cycle regulators and signal transduction mols., was differentially affected by the **treatment**. The present study indicates the involvement of an addnl. cascade of events that might act in parallel to oxidative stress and **inflammation** to converge eventually into a common pathway leading to neurodegeneration. The attenuation of these gene changes by R-apomorphine, an iron chelator-radical scavenger drug, supports our previous findings in vivo where R-apomorphine was neuroprotective.

RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 26 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 135:41038 CA
TI Methods of **treating** central nervous system ischemic or hemorrhagic injury using anti alpha4 integrin antagonists
IN Relton, Jane; Lobb, Roy; Whalley, Eric; Adams, Steve
PA Biogen, Inc., USA
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001043774	A1	20010621	WO 2000-US33942	20001214
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1242118	A1	20020925	EP 2000-984395	20001214
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003517023	T2	20030520	JP 2001-544910	20001214
	US 2002197233	A1	20021226	US 2002-170841	20020613
PRAI	US 1999-171265P	P	19991216		
	WO 2000-US33942	W	20001214		

AB Methods of, and compns. for, **treating** central nervous system injury with an antagonist of an alpha4 subunit contg. integrin are described.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 27 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 134:300800 CA
TI Compositions for **treating** neurobehavioral disorders
IN Bechthold, Joyce Corinne; Lilly, Thomas Duff
PA USA
SO PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001026642	A2	20010419	WO 2000-US27894	20001006
	WO 2001026642	A3	20020510		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV,				

MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-158604P P 19991008
US 1999-164049P P 19991108
US 1999-166068P P 19991117
US 2000-201043P P 20000501

AB This compn. is for **treating** neurobehavioral disorders, by restoring normal neurotransmitter, receptor, transport and metabolic function. The first stage of **treatment** is to administer an i.v. compn. designed to **treat** the patient symptoms. The next stage is supplemental oral support. This invention embodies compns. for i.v. **treatment** of certain types of neurobiol. disorders and methods of diagnosis, which comprises specialized testing and pre-diagnosis of underlying neurol. conditions, immunization, and methods of education and psychol. support available remotely through the Internet or by mail. Thus, an i.v. soln. contains at least 1 amino acid, vitamin C and electrolytes and a corticosteroid.

L6 ANSWER 28 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 134:250648 CA
TI Neurotransmitter and **inflammatory** correlates in experimental neuropathy: Modulation by electric spinal cord stimulation
AU Linderoth, Bengt; Cui, Jian-Guo; Yakhnitsa, Vadym; Shi, T. -J. Sten; Stiller, Carl-Olav; O'Connor, William T.; Holmin, Staffan; Mathiesen, Tiit; Sollevi, Alf; Hokfelt, Tomas; Meyerson, Bjorn A.
CS Department of Clinical Neuroscience, Section of Neurosurgery, Karolinska Institute, Stockholm, S-171 76, Swed.
SO Pain and Neuroimmune Interactions, [Proceedings of an International Symposium on Pain and Neuroimmune Interactions], Beirut, Lebanon, May 12-13, 1999 (2000), Meeting Date 1999, 57-68. Editor(s): Saade, Nayef E.; Apkarian, A. Vania; Jabbur, Suhayl J. Publisher: Kluwer Academic/Plenum Publishers, New York, N. Y.
CODEN: 69AQJQ
DT Conference
LA English
AB Neuropathic pain is often difficult to manage with pharmacotherapy but may be effectively relieved by elec. stimulation of the spinal cord (SCS). This mode of **treatment** has been practiced for more than three decades, but the knowledge about the mechanisms involved in the pain alleviating effect is still fragmentary. Injury of a peripheral nerve induces multiple pathol. changes in the peripheral nerve itself, in the dorsal root ganglion (DRG) and in the dorsal horn (DH) of the spinal cord. It may further result in the development of neuropathic symptoms including, besides chronic pain, hypersensitivity to peripheral stimuli (allodynia, dysaesthesia and hyperalgesia). Local **inflammatory** changes in a lesioned nerve become evident a short time after the injury, as indicated by local upregulation of macrophages and their secretory products interleukin-6 and TNF-.alpha.. In exptl. animals, these changes appear to relate to the development of hypersensitivity to peripheral stimuli, a sign which is similar to the allodynia obsd. in patients after nerve injury. The behavioral changes noted after exptl. nerve lesion seem to be related to hypersensitization of wide-dynamic range neurons (WDR) in the dorsal horn, characterized by increased spontaneous activity and after-discharges following application of innocuous stimuli to their receptive fields. The state of neuronal hyperexcitability is also mirrored by marked changes in neurotransmitter functions in the DH as well as in the DRG. When SCS, with similar stimulation parameters as used in the clinic, is applied in an animal with exptl. neuropathy, the alleviation of hypersensitivity to innocuous stimuli is accompanied by significant decreases in the pathol. elevated basal levels of glutamate and aspartate in the DH. Recent studies indicate that this effect is mediated via **GABA**-B receptor activation. Alterations in the adenosine system may also be involved - as well as other substances like glycine, 5-HT, noradrenaline and substance P, which have been demonstrated to be spinally released with SCS. Increased knowledge about the

pathophysiol. of nerve injury, the neurochem. mechanisms involved in the beneficial effects of SCS and the manipulation of these effects can form a basis for combining pharmacol. regimens with electrostimulation in order to enhance their therapeutic efficacy. Data from clin. pilot trials are reported.

RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 29 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 134:192604 CA
TI Physiopathology of symptomatic and latent forms of central nervous hyperexcitability due to magnesium deficiency: a current general scheme
AU Durlach, Jean; Bac, Pierre; Bara, Michel; Guiet-Bara, Andree
CS SDRM, Hopital Saint-Vincent-de-Paul, Paris, F-75014, Fr.
SO Magnesium Research (2000), 13(4), 293-302
CODEN: MAGREF; ISSN: 0953-1424
PB John Libbey & Co. Ltd.
DT Journal; General Review
LA English
AB A review with 64 refs. Symptomatic forms of central nervous hyperexcitability (NHE) due to magnesium deficiency results from the sum of direct cellular effects and of local and systemic mediated effects inducing depolarization and NHE. Direct effects assoc. decreased energy and cationic gradient with disturbances in Ca distribution, decreased second messenger nucleotidic ratio and increased susceptibility to peroxidn. Local mediated effects assoc. increased activity of excitatory neuromediators: acetylcholine, catecholamines and ionotropic - (NMDA and non-NMDA) - receptors of excitatory amino acids (EAA), with decreased activity of inhibitory neuromediators: **GABA**, taurine, glutaurine, adenosine and K receptors of opioids. Systemic mediated effects assoc. increased prodn. of **inflammatory** mediators: neuropeptides, prostanoids, cytokines Th 1, aldehydes with decreased activity of oxidant and antialdehyde defences. Compensatory factors instrumental in the latency of NHE due to magnesium deficiency may also be direct or mediated. Increased intracellular pH, modifications of Ca and Mg binding proteins, increase in "magnesium-like" polyamines, stimulation of cellular antioxidant system; decreased activity of EAA metabotropic receptors and of opioid mu (and delta) receptors, increased activity of inhibitory neuromediators, increased prodn. of anti-**inflammatory** mediator such as cytokines Th 2, stimulation of systemic antioxidant and antialdehyde defences. A lot of diverse compds. are able to palliate symptomatic NHE due to magnesium deficiency either by pharmacodynamic effects or through physiopathol. intervention. The efficiency of these **treatments** can be evaluated on multiple disparate parameters. The pattern of NHE due to magnesium deficiency differs according to species, strains, gender, age and intensity of magnesium deficiency. For example, hot plate test showed a hypoalgesia "morphine-like" pattern induced by magnesium deficiency cured by magnesium acetyltaurinate in mice while paw pressure test showed a hyperalgic pattern caused by magnesium deficiency cured by dizolcipine in rats. Now it seems difficult to rank hierarchically the various physiopathol. mechanisms of NHE due to magnesium deficiency. But the proposed general scheme of the factors controlling this NHE provides a possible explanation of both diffuse symptomatic and latent forms and stresses the complexity of the physiopathol. mechanisms of central NHE due to magnesium deficiency.

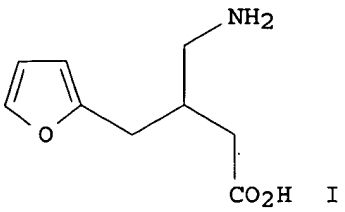
RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 30 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 134:29300 CA
TI Preparation of 3-heteroarylalkyl substituted **GABA** analogs as anticonvulsants
IN Yuen, Po-Wai
PA Warner-Lambert Company, USA
SO PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000073296	A2	20001207	WO 2000-US11397	20000428
	WO 2000073296	A3	20010719		
	W: AE, AG, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	BR 2000011039	A	20020226	BR 2000-11039	20000428
	EP 1185524	A2	20020313	EP 2000-928498	20000428
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2003500486	T2	20030107	JP 2000-621362	20000428
PRAI	US 1999-136491P	P	19990528		
	WO 2000-US11397	W	20000428		

OS MARPAT 134:29300

GI



I

AB Title compds. [RCH2CH(CH2NH2)CH2COOH; R = thiophenyl, furanyl, pyrrolyl] are prepd. and are useful in the **treatment** of epilepsy, faintness attacks, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathol. disorders, gastrointestinal disorders such as irritable bowel syndrome (IBS), and **inflammation**, esp. arthritis. A pharmaceutical compn. contg. a compd. of title compd. as well as methods of prepg. the compds. and novel intermediates useful in the prepn. of the final compds. are included. Thus, the title compd. I was prepd. and tested in mice for prevention of audiogenic seizures.

L6 ANSWER 31 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 133:344633 CA
TI Modulation of substance P by **GABA** analogs, and therapeutic methods
IN Magistro, Philip John, Jr.
PA Warner-Lambert Company, USA
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000067742	A2	20001116	WO 2000-US6199	20000310
	WO 2000067742	A3	20010816		
	W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
PRAI	US 1999-132614P	P	19990505		

OS MARPAT 133:344633

AB Modulation of substance P by **GABA** analogs is disclosed. Preferred **GABA** analog compds. include gabapentin and pregabalin.

Methods of the invention include the modulation of substance P, as well as methods for preventing or **treating** conditions assocd. with substance P, by administering to an animal an effective amt. of one or more **GABA** analog compds. Conditions assocd. with substance P include headaches and migraine, neurogenic **inflammation**, emesis, nausea and vomiting, cough and bronchitis, obesity, allergy, asthma, hemorrhoids and anal fissures, ulcer, fever, infertility and periodontal disease.

L6 ANSWER 32 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 133:290816 CA
TI Brain levels of inhibitory and excitatory amino acids in response to non steroidal anti-**inflammatory** drugs
AU Samaan, Hany A.; El-Mageed, Fayez A. Abd
CS National Organization for Drug Control and Research, Cairo, Egypt
SO Egyptian Journal of Pharmaceutical Sciences (1999), Volume Date 1998, 39(1-3), 45-56
CODEN: EJPSBZ; ISSN: 0301-5068
PB National Information and Documentation Centre
DT Journal
LA English
AB The neuronal inhibitory amino acids glycine (GLY), gamma aminobutyric acid (**GABA**), and taurine (TAU) as well as the excitatory acidic amino acids aspartate (ASP) and glutamate (GLU) were reported to delineate several central drugs actions and toxic side effects. Nonsteroidal antiinflammatory drugs (NSAIDS) posses central or partly central antipyretic and analgesic actions. In the present work, the subcortical brain levels of both inhibitory and excitatory amino acids were detd. in rats orally **treated** with either saline, acetyl salicylic acid, piroxicam or pirprofen. Two doses of each compd. were used, corresponding to av. therapeutic and over dosage levels. The results indicated the probable differential involvement of the inhibitory amino acids in the partly central analgesic and antipyretic actions of these NSAIDS. The acidic excitatory amino acids are probably involved in the over dosage side effects of these agents. The future utilization of such findings in enhancing the efficacy and lowering the toxicity of NSAIDS is discussed.
RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 33 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 133:276359 CA
TI GABAB receptor ligands for increasing neurotrophin levels, and therapeutic use thereof
IN Bernasconi, Raymond; Otten, Uwe
PA Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SO PCT Int. Appl., 10 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000057862	A2	20001005	WO 2000-EP2605	20000323
WO 2000057862	A3	20010809		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1143942	A2	20011017	EP 2000-914167	20000323
EP 1143942	A3	20020911		
EP 1143942	B1	20030813		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

	AT 246922	E	20030815	AT 2000-914167	20000323
	US 2002013257	A1	20020131	US 2001-955381	20010918
PRAI	GB 1999-6882	A	19990325		
	WO 2000-EP2605	W	20000323		

AB Ligands to GABAB receptors are used for increasing neurotrophin levels in the central nervous system. These ligands can be used in the **treatment** of conditions responsive to an increase of neurotrophin levels in the central nervous system, e.g. neurodegenerative diseases.

L6 ANSWER 34 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 133:182988 CA
TI Organosilicate sol-gel matrixes for drug delivery
IN Babich, John W.; Bonavia, Grant; Zubieta, Jon
PA Biostream, Inc., USA
SO PCT Int. Appl., 133 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000047236	A1	20000817	WO 2000-US3754	20000214
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2328614	AA	20000817	CA 2000-2328614	20000214
	US 6395299	B1	20020528	US 2000-503438	20000214
	JP 2002536422	T2	20021029	JP 2000-598187	20000214
	US 2003082238	A1	20030501	US 2002-77475	20020215
PRAI	US 1999-119828P	P	19990212		
	US 2000-503438	A1	20000214		
	WO 2000-US3754	W	20000214		

AB Biocompatible matrixes such as sol-gels encapsulating a reaction center may be administered to a subject for conversion of prodrugs into biol. active agents. In certain embodiments, the biocompatible matrixes of the present invention are sol-gels. In one embodiment, the enzyme L-amino acid decarboxylase is encapsulated and implanted in the brain to convert L-dopa to dopamine for **treatment** of Parkinson's disease. The silica sol was prepd. by the addn. of substituted trimethoxysilanes, tetra-Me orthosilicate (TMOS) and 4 mM HCl soln. Total desired vol. of the sol was detd. by the no. of matrixes to be prepd. Entrapment of penicillinase in the matrix was performed by using pH 6.5 phosphate buffer. The penicillinase activity was detd. by using 3 mM soln. of penicillin G in buffer.

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 35 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 133:129369 CA
TI Cellular actions of opioids and other analgesics: implications for synergism in pain relief
AU Christie, MacDonald J.; Connor, Mark; Vaughan, Christopher W.; Ingram, Susan L.; Bagley, Elena E.
CS The Medical Foundation, The University of Sydney, Sydney, 2006, Australia
SO Clinical and Experimental Pharmacology and Physiology (2000), 27(7), 520-523
CODEN: CEXPB9; ISSN: 0305-1870
PB Blackwell Science Asia Pty Ltd.
DT Journal; General Review
LA English
AB A review with 31 refs. 1. .mu.-Opioid receptor agonists mediate their central analgesic effects by actions on neurons within brain regions such as the mid-brain periaqueductal gray (PAG). Within the PAG, .mu.-opioid

receptor-mediated analgesia results from inhibition of GABAergic influences on output projection neurons. The authors have established that .mu.-opioid receptor activation in the PAG causes a presynaptic inhibition of **GABA** release that is mediated by activation of a voltage-dependent K+ channel via 12-lipoxygenase (LOX) metabolites of arachidonic acid. 2. At a cellular level, .mu.-opioid agonists have also been shown to open inwardly rectifying K+ channels, close voltage-gated Ca2+ channels and presynaptically inhibit glutamatergic synaptic transmission in the PAG. 3. The .mu.-opioid receptor-mediated presynaptic inhibition of GABAergic transmission was abolished by phospholipase A2 inhibitors and non-specific LOX and specific 12-LOX inhibitors. Cyclo-oxygenase (COX) and specific 5-LOX inhibitors did not reduce the inhibitory effects of .mu.-opioid agonists. 4. The opioid actions on GABAergic transmission were mimicked by arachidonic acid and 12-LOX metabolites, but not 5-LOX metabolites. The efficacy of .mu.-opioids was enhanced synergistically by **treatment** of PAG neurons with inhibitors of the other major enzymes responsible for arachidonic acid metab., COX and 5-LOX. 5. These results explain a previously described analgesic action of COX inhibitors in the central nervous system that was both independent of prostanoid release and inhibited by opioid receptor antagonists and they also explain the synergistic interaction of opioids with COX inhibitors. These findings also suggest new avenues for the development of centrally active analgesic agents involving combinations of lowered doses of opioids and specific 5-LOX inhibitors.

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 36 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 132:339382 CA
TI Combination of a **GABA**-A .alpha.-5 inverse agonist and Cox-2 inhibitor, NSAID, estrogen or vitamin E
IN Block, Gilbert A.; Lines, Christopher R.
PA Merck & Co., Inc., USA
SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000027382	A2	20000518	WO 1999-US26623	19991110
	WO 2000027382	A3	20000831		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1131102	A2	20010912	EP 1999-960268	19991110
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	US 6440967	B1	20020827	US 1999-438007	19991110
	JP 2002529406	T2	20020910	JP 2000-580611	19991110
PRAI	US 1998-108105P	P	19981112		
	GB 1999-1338	A	19990121		
	WO 1999-US26623	W	19991110		

AB Combinations of a GABAA alpha 5 inverse agonist and a COX-2 inhibitor, NSAID, estrogen or vitamin E are disclosed for **treatment** of neurodegenerative conditions such as Alzheimer's disease. 3-(5-Methylisoxazol-3-yl)-6-(1-methyl-1,2,3-triazol-4-yl)methoxy-1,2,4-triazolo[3,4-a]phthalazine (I), a GABAA-.alpha.5 inverse agonist, was prepd. by a series of reactions. Thus, tablets contained I 50.0, microcryst. cellulose 80.0, modified corn starch 80.0, lactose 189.5, and Mg stearate 0.5 mg/tablet.

L6 ANSWER 37 OF 75 CA COPYRIGHT 2003 ACS on STN

AN 132:264102 CA
TI Transplantation of neural cells for the **treatment** of chronic pain or spasticity
IN Dinsmore, Jonathan; Siegan, Julie
PA Diacrin, Inc., USA
SO PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000018413	A1	20000406	WO 1999-US21084	19990915
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 2001055587	A1	20011227	US 1998-163684	19980930
US 6444205	B2	20020903		
CA 2346005	AA	20000406	CA 1999-2346005	19990915
AU 9962478	A1	20000417	AU 1999-62478	19990915
AU 747862	B2	20020523		
EP 1117413	A1	20010725	EP 1999-949647	19990915
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI US 1998-163684	A	19980930		
WO 1999-US21084	W	19990915		

AB Methods for using neural cells to **treat** chronic pain and/or spasticity are described. The neural cells can be derived from any mammal, and are preferably human or porcine in origin. The neural cells preferably are serotonergic cells or are gamma-aminobutyric acid (**GABA**)-producing cells. Neural cells can be obtained from adult, juvenile, embryonic or fetal donors. Neural cells can be modified to be suitable for transplantation into a subject. For example, the neural cells can be modified such that an antigen (e.g., an MHC class I antigen) on the cell surface which is capable of stimulating an immune response against the cell in a subject is altered (e.g., by contact with an anti-MHC class I antibody, or a fragment or deriv. thereof) to inhibit rejection of the cell when introduced into the subject or can be genetically modified to produce a factor. In one embodiment, the neural cells are obtained from a pig which is essentially free from organisms or substances which are capable of transmitting infection or disease to the recipient subject. The neural cells of the present invention can be used to **treat** chronic pain and/or spasticity by delivering the cells into the spinal cord or a subject.
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 38 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 132:146983 CA
TI Effects of **GABA** receptor antagonist on trigeminal caudalis nociceptive neurons in normal and neonatally capsaicin-**treated** rats
AU Chiang, Chen Yu; Kwan, Chun L.; Hu, James W.; Sessle, Barry J.
CS Faculty of Dentistry, University of Toronto, Toronto, ON, M5G 1G6, Can.
SO Journal of Neurophysiology (1999), 82(5), 2154-2162
CODEN: JONEA4; ISSN: 0022-3077
PB American Physiological Society
DT Journal
LA English
AB Effects of **GABA** receptor antagonist on trigeminal caudalis nociceptive neurons in normal and neonatally capsaicin-**treated** rats. The authors have recently demonstrated that significant increases in cutaneous mechanoreceptive field (RF) size and spontaneous activity occur in nociceptive neurons of trigeminal subnucleus caudalis (Vc, the medullary dorsal horn) of adult rats depleted of C-fiber afferents by neonatal **treatment** with capsaicin. These neuronal changes in capsaicin-**treated** (CAP) rats are suggestive of central neuroplasticity and involve N-methyl-D-aspartic acid (NMDA) receptor mechanisms. The present study examd. whether the GABAA receptor

antagonist bicuculline (BIC) or the GABAB receptor antagonist 2-hydroxysaclofen (SAC) can influence the RF properties and activity of Vc nociceptive neurons classified as either nociceptive-specific or wide-dynamic range in CAP adult rats or in neonatally vehicle-**treated** (CON) rats. C-fiber depletion was confirmed in the CAP rats by a significant decrease in plasma extravasation of Evans blue dye in a skin area receiving topical application of mustard oil, a small-fiber excitant and **inflammatory** irritant. As previously reported, marked increases in cutaneous RF size and spontaneous activity occurred in Vc nociceptive neurons of adult CAP rats, compared with CON rats. GABAA receptor blockade by BIC (i.t.) in CON rats produced a significant increase in spontaneous activity and in pinch RF size and tactile RF size (or appearance of a tactile area in the RF of nociceptive-specific neurons), as well as a significant lowering of the mech. threshold and a significant enhancement of responses to pinch stimuli applied to the RF. In CAP rats, GABAA receptor blockade also produced significant changes similar to those documented in CON rats, except for a paradoxical and significant decrease in pinch RF size and no noticeable changes in responses to pinch stimuli. GABAB receptor blockade by SAC (i.t.) did not produce any significant changes in Vc nociceptive neurons in either CON or CAP rats. These results suggest that GABAA receptor-mediated inhibition may be involved in maintaining the functional expression of Vc nociceptive neuronal properties in normal conditions, and that in animals depleted of their C-fiber afferents, some features of this GABAA receptor-mediated modulation may be disrupted such that a GABAA receptor-mediated excitation is manifested.

RE.CNT 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 39 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 132:134697 CA
TI Toxic activities of sesquiterpene lactones: Structural and biochemical aspects
AU Schmidt, Thomas J.
CS Institut fur Pharmazeutische Biologie der Heinrich-Heine, Universitat Dusseldorf, Dusseldorf, D-40225, Germany
SO Current Organic Chemistry (1999), 3(6), 577-608
CODEN: CORCFE; ISSN: 1385-2728
PB Bentham Science Publishers
DT Journal; General Review
LA English
AB A review with 251 refs. As one of the largest groups of secondary plant metabolites, sesquiterpene lactones (STL) possess a broad variety of conspicuous biol. activities directed towards all types of predating organisms. The majority of these compds. are believed to exert their activities by a common chem. mechanism of action, alkylation of biol. macromols. leading to decisive consequences on cellular function. An impressive no. of enzymes and other essential macromols. are known to be inhibited by STL, usually at very low concns. Such alkylant STL, therefore, are generally cytotoxic. Although many of them possess potentially useful activities, e.g. as therapeutic agents against **inflammation** and cancer, the low selectivity of these effects usually forbids utilization due to high unspecific toxicity. In addn. to such alkylants which can be considered a non-specific and highly efficient chem. weapon against literally any organism that might be harmful to the plants, some less common representatives which exert toxicity by very specific mol. mechanisms, such as some strong inhibitors of intracellular calcium signalling and some highly potent **GABA**-antagonistic neurotoxins, are **treated** sep. The various aspects of sesquiterpene lactone toxicity from the general chem. basis via mol. targets and toxic effects at the cellular level to toxicity vs. the different mammalian organ systems are outlined. Wherever possible, special attention is paid to relationships between chem. structure and bioactivity.

RE.CNT 256 THERE ARE 256 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 40 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 132:132347 CA

TI Cyclodextrins, alone or combined with other agents, for the **treatment** of cerebral ischemia or central nervous system injury
IN Nelson, Alan John
PA Cerebrus Pharmaceuticals Limited, UK
SO PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000004888	A2	20000203	WO 1999-GB2311	19990719
WO 2000004888	A3	20000427		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9950508	A1	20000214	AU 1999-50508	19990719
PRAI GB 1998-15785	A	19980720		
WO 1999-GB2311	W	19990719		

AB A substituted or unsubstituted cyclodextrin is used as the active agent in the manuf. of a medicament for the **treatment** of cerebral ischemia or central nervous system injury. The cyclodextrin may be combined with a second drug useful in the **treatment** of cerebral ischemia or central nervous system injury. The effect of 2-hydroxypropyl-.beta.-cyclodextrin in a cerebral ischemia model is described.

L6 ANSWER 41 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 132:102843 CA
TI **GABA** analogs for preventing and **treating** gastrointestinal damage
IN Guglietta, Antonio; Taylor, Charles Price, Jr.; Ren, Jiayuan; Watson, W. P.; Rafferty, Michael Francis; Diop, Laurent; Chovet, Maria; Bueno, Lionel; Little, Hilary J.
PA Jouveinal, Fr.
SO Eur. Pat. Appl., 20 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 974351	A2	20000126	EP 1998-401018	19980424
EP 974351	A3	20001213		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRAI EP 1998-401018		19980424

OS MARPAT 132:102843
AB **GABA** analogs are useful to prevent and **treat** gastrointestinal damage and ethanol withdrawal syndrome. Preferred **treatments** employ gabapentin or pregabalin.

L6 ANSWER 42 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 132:44423 CA
TI Honokiol and magnolol increase the number of [3H]muscimol binding sites three-fold in rat forebrain membranes in vitro using a filtration assay, by allosterically increasing the affinities of low-affinity sites
AU Squires, Richard F.; Ai, Jinglu; Witt, Michael-Robin; Kahnberg, Pia; Saederup, Else; Sterner, Olov; Nielsen, Mogens
CS Center for Neurochemistry, The Nathan Kline Institute for Psychiatric Research Orangeburg, NY, 10962, USA
SO Neurochemical Research (1999), 24(12), 1593-1602
CODEN: NEREDZ; ISSN: 0364-3190

PB Kluwer Academic/Plenum Publishers
DT Journal
LA English
AB 1. The bark of the root and stem of various Magnolia species has been used in Traditional Chinese Medicine to **treat** a variety of disorders including anxiety and nervous disturbances. The biphenolic compds. honokiol (H) and magnolol (M), the main components of the Chinese medicinal plant Magnolia officinalis, interact with GABAA receptors in rat brain in vitro. The authors compared the effects of H and M on [3H]muscimol (MUS) and [3H]flunitrazepam (FNM) binding using EDTA/water dialyzed rat brain membranes in a buffer contg. 150 mM NaCl plus 5 mM Tris-HCl, pH 7.5 as well as [35S]t-butylbicyclophosphorothionate (TBPS) in 200 mM KBr plus 5 mM Tris-HCl, pH 7.5. H and M had similar enhancing effects on [3H]MUS as well as on [3H]FNM binding to rat brain membrane prepns., but H was 2.5 to 5.2 times more potent than M. **GABA** alone almost doubled [3H]FNM binding with EC50 = 450 nM and 200 nM using forebrain and cerebellar membranes, resp. In the presence of 5 .mu.M H or M the EC50 values for **GABA** were decreased to 79 and 89 nM, resp., using forebrain, and 39 and 78 nM, using cerebellar membranes. H and M potently enhanced the potentiating effect of 200 nM **GABA** on [3H]FNM binding with EC50 values of 0.61 .mu.M and 1.6 .mu.M using forebrain membranes, with maximal enhancements of 33 and 47%, resp. Using cerebellar membranes, the corresponding values were 0.25 and 1.1 .mu.M, and 22 and 34%. H and M increased [3H]MUS binding to whole forebrain membranes about 3-fold with EC50 values of 6.0 and 15 .mu.M. Using cerebellar membranes, H and M increased [3H]MUS binding .apprx.68% with EC50 values of 2.3 and 12 .mu.M, resp. Scatchard anal. revealed that the enhancements of [3H]MUS binding were due primarily to increases in the no. of binding sites (Bmax values) with no effect on the high affinity binding consts. (Kd values). The enhancing effect of H and M were not additive. H and M displaced [35S]TBPS binding from sites on whole rat forebrain membranes with IC50 values of 7.8 and 6.0 .mu.M, resp. Using cerebellar membranes, the corresponding IC50 values were 5.3 and 4.8 .mu.M. These inhibitory effects were reversed by the potent GABAA receptor blocker R5135 (10 nM), suggesting that H and M allosterically increase the affinity of GABAA receptors for **GABA** and MUS by binding to sites in GABAA receptor complexes. Two monophenols, the anesthetic propofol (2,6-diisopropylphenol, P) and the anti-**inflammatory** diflunisal (2',4'-difluoro-4-hydroxy-3-biphenyl carboxylic acid, D) also enhanced [3H]MUS binding, decreased the EC50 values for **GABA** in enhancing [3H]FNM binding and potentiated the enhancing effect of 200 nM **GABA** on [3H]FNM binding, although enhancements of [3H]MUS binding for these monophenols were smaller than those for H and M, using forebrain and cerebellar membranes. The enhancing effect of P and D on [3H]MUS binding were almost completely additive. 2,2'-Biphenol was inactive on [3H]MUS and [3H]FNM binding. These, and other preliminary expts., suggest that appropriate ortho (C2) and para (C4) substitution increases the **GABA**-potentiating activity of phenols. The potentiation of GABAergic neurotransmission by H and M is probably involved in their previously reported anxiolytic and central depressant effects.
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 43 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 131:168702 CA
TI Peripheral **inflammation** is associated with decreased veratridine-induced release of **GABA** in the rat ventrocaudal periaqueductal gray: microdialysis study
AU Renno, Waleed M.; Beitz, Alvin J.
CS Abha Branch, Department of Anatomy, College of Medicine, King Saud University, Abha, Saudi Arabia
SO Journal of the Neurological Sciences (1999), 163(2), 105-110
CODEN: JNSCAG; ISSN: 0022-510X
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
AB Systemic administration of opiates or direct injection of opioid peptides into the periaqueductal gray (PAG) produces a profound antinociception which is thought to be assocd. with inhibition of neuronal activity in the

PAG. This inhibitory effect has been postulated to result from opiate inhibition of GABAergic neurons in the PAG. Whether this opioid-GABAergic system is affected in acute pain state has not been investigated. The present study was thus designed to det. the effects of unilateral peripheral **inflammation** on ventrocaudal PAG .gamma.-aminobutyric acid (**GABA**) release in the rat using in vivo microdialysis and subsequent high pressure liq. chromatog. (HPLC) anal. Microdialysis was chosen to perform direct and dynamic studies of amino acid concns. in the PAG in control rats and in animals subjected to acute and prolonged **inflammation** caused by injection of 120 .mu.l of Complete Freund's Adjuvant (CFA) into the hind paw. **GABA** release was significantly decreased in the CFA **treated** groups both 24 h as well as 7 days post-**treatment**. **GABA** release decreased to approx. one-fourth that of the 24 h mineral oil control group. Likewise, veratridine-induced release of **GABA** was decreased in rats **treated** with CFA 7 days prior to dialysis. Systemic injection of naloxone (5 mg/kg i.p.) caused selective and significant block in the decrease of veratridine-induced release of **GABA** in the 24 h CFA-**treated** rats. Taken together with data from our previous studies, these results suggest that the decrease in veratridine-induced **GABA** release in this study may be due to an increase opiate inhibition of **GABA** resulting from the induction of acute or prolonged elevation of nociceptive input.

RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 44 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 131:168353 CA
TI Identification of loci involved in accelerated wound healing and the development of new wound healing promoters
IN Heber-Katz, Ellen
PA The Wistar Institute, USA
SO PCT Int. Appl., 136 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9941364	A2	19990819	WO 1999-US2962	19990212
	WO 9941364	A3	19991223		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2319700	AA	19990819	CA 1999-2319700	19990212
	AU 9926720	A1	19990830	AU 1999-26720	19990212
	EP 1053309	A1	20001122	EP 1999-906924	19990212
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2002503460	T2	20020205	JP 2000-531545	19990212
	US 2003037345	A1	20030220	US 1999-249155	19990212
	US 6538173	B2	20030325		
PRAI	US 1998-74737P	A2	19980213		
	US 1998-97937P	A2	19980826		
	US 1998-102051P	A2	19980928		
	WO 1999-US2962	W	19990212		

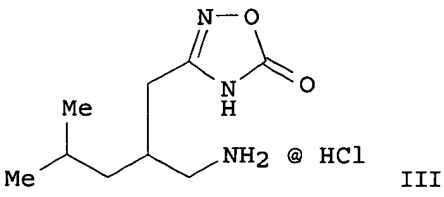
AB Genes that quant. improve the efficiency and effectiveness of wound healing in mice are identified. Wound healing is assayed by measuring the time taken for a 2 mm hole punched into the ear to heal. The genes or gene products may be useful in the development of new wound healing promoters, including agents for **treatment** of central and peripheral nerve wounds. Wound healing in the rapidly healing mouse line MRL was studied. In comparison to the C57BL/6 line, the MRL mice showed

more extensive vascularization around wounds with rapid development of sebaceous glands and hair follicles and the unexpected appearance of adipocytes. These mice also showed improved healing of damage to the optic and sciatic nerve after crushing, and of the spinal cord after complete transection. Using the difference in wound healing behavior of the two lines, genetic polymorphisms assocd. with QTLs affecting wound healing were identified. The accelerated healing of the MRL line was lost with aging, and this appeared to be as a result of T-cell actions. Macrophages from the MRL accelerated wound healing in control mice.

L6 ANSWER 45 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 131:58836 CA
TI Preparation of novel, gabapentin-related amines as pharmaceutical agents
IN Belliotti, Thomas Richard; Bryans, Justin Stephen; Capiris, Thomas; Horwell, David Christopher; Kneen, Clare Octavia; Wustrow, David Juergen
PA Warner-Lambert Co., USA
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9931074	A2	19990624	WO 1998-US23917	19981110
	WO 9931074	A3	19991104		
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2304965	AA	19990624	CA 1998-2304965	19981110
	AU 9917962	A1	19990705	AU 1999-17962	19981110
	AU 759619	B2	20030417		
	BR 9813656	A	20001010	BR 1998-13656	19981110
	EP 1045839	A2	20001025	EP 1998-962805	19981110
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002508361	T2	20020319	JP 2000-539001	19981110
	NZ 503981	A	20021220	NZ 1998-503981	19981110
	ZA 9811464	A	19990615	ZA 1998-11464	19981214
	ZA 9811474	A	19990615	ZA 1998-11474	19981214
	ZA 9811472	A	19990707	ZA 1998-11472	19981214
	US 6521650	B1	20030218	US 2000-509917	20000404
	NO 2000003037	A	20000614	NO 2000-3037	20000614
PRAI	US 1997-69773P	P	19971216		
	US 1998-104924P	P	19981020		
	WO 1998-US23917	W	19981110		

OS MARPAT 131:58836
GI



III

AB H2NCH2CH(CH2CHMe2)(CH2)nR (I; R = sulfonamide, amide, phosphonic acid, heterocycle, sulfonic acid or hydroxamic acid residue; n = 0-2) and H2NCH2CAB(CH2)nR [II; A = H, Me; B = cycloalkyl(alkyl), C1-11 alkyl, etc.; R, n as above] or their pharmaceutically acceptable salts, useful as agents in the **treatment** of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression,

anxiety, panic, pain, neuropathol. disorders, **inflammatory** diseases, and gastrointestinal disorders, were prepd. Processes for the prepn. of I and II and intermediates useful in the prepn., and approx 10 specific I and II are also claimed. For example, amidation in DMF of Me2CHCH2O2CCl with partially protected amidoxime BOC-NHCH2(CH2CHMe2)CH2C(:NOH)NH2 [5-step prepn. from the racemic H2NCH2CH(CH2CHMe2)CH2CO2H given], cyclization of the resulting carbamate by refluxing for 2 h in xylene and deprotection/salification with 4M HCl in dioxane gave a title amine salt III. In radioligand binding assay to .alpha.2.delta. subunit derived from porcine brain tissue III had IC50 1.52 .mu.M, vs. 0.10-0.12 .mu.M for gabapentin.

L6 ANSWER 46 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 131:714 CA
TI Therapeutic uses of triazolo-pyridazine derivatives
IN Castro Pineiro, Jose Luis; Hefti, Franz Fridolin; Hill, Raymond George; McKernan, Ruth; Tattersall, Frederick David; Whiting, Paul John
PA Merck Sharp & Dohme Limited, UK
SO PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9925353	A1	19990527	WO 1998-GB3328	19981106
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9910415	A1	19990607	AU 1999-10415	19981106
	US 6174886	B1	20010116	US 1998-191304	19981112
	US 6107296	A	20000822	US 1998-206416	19981207
	US 6110915	A	20000829	US 1998-208288	19981208
	US 6046196	A	20000404	US 1998-208291	19981209
	US 6063783	A	20000516	US 1998-209071	19981210
PRAI	GB 1997-23999	A	19971113		
	GB 1997-26699	A	19971218		
	GB 1997-26700	A	19971218		
	GB 1997-26701	A	19971218		
	GB 1997-26702	A	19971218		
	GB 1998-1581	A	19980123		
	WO 1998-GB3328	W	19981106		

OS MARPAT 131:714
AB A class of substituted or 7,8-ring fused 1,2,4-triazolo[4,3-b]pyridazine derivs., possessing an optionally substituted cycloalkyl, Ph or heteroaryl substituent at the 3-position and a substituted alkoxy moiety at the 6-position, are selective ligands for GABAA receptors, in particular having high affinity for the .alpha.2 and/or .alpha.3 subunit thereof, and are accordingly of benefit in the **treatment** and/or prevention of psychotic disorders including schizophrenia; neurodegeneration arising from cerebral ischemia; pain; emesis; and muscle spasm or spasticity, e.g. in paraplegic patients.
RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 47 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 130:329183 CA
TI Pharmaceutical grade valerian, black cohosh, vitex agnus-castus, bilberry and milk thistle, and method for determining thereof
IN Khwaja, Tasneem A.; Friedman, Elliot P.
PA Pharmaprint, Inc., USA; University of Southern California
SO PCT Int. Appl., 138 pp.
CODEN: PIXXD2
DT Patent

LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9921006	A1	19990429	WO 1998-US22505	19981023
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US, US, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2307339	AA	19990429	CA 1998-2307339	19981023
AU 9913632	A1	19990510	AU 1999-13632	19981023
PRAI US 1997-955410	A2	19971023		
US 1997-955417	A2	19971023		
US 1997-956610	A2	19971023		
US 1997-956611	A2	19971023		
US 1997-956615	A2	19971023		
WO 1998-US22505	W	19981023		

AB The present invention relates generally to botanical valerian materials and methods for making such materials in medicinally useful and pharmaceutically acceptable forms. More particularly, the present invention relates to the use of compositional and bioactivity fingerprints in the processing of valerian, black cohosh, V. agnus-castus, bilberry or milk thistle materials to produce botanical products, such as drugs, which qualify as pharmaceutical grade compns. which are suitable for use in clin. or veterinary settings to **treat** and/or ameliorate diseases, disorders or conditions.

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 48 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 130:316593 CA
TI Pharmaceutical grade ginseng
IN Khwaja, Tasneem A.; Friedman, Elliot P.
PA Pharmaprint, Inc., USA; University of Southern California
SO PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9920292	A1	19990429	WO 1998-US22510	19981023
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2307047	AA	19990429	CA 1998-2307047	19981023
AU 9911183	A1	19990510	AU 1999-11183	19981023
JP 2001521876	T2	20011113	JP 2000-516689	19981023
PRAI US 1997-956616	A2	19971023		
WO 1998-US22510	W	19981023		

AB Ginseng materials and methods for making such materials in medicinally useful and pharmaceutically acceptable forms are claimed. More particularly, the present invention relates to the use of compositional and activity fingerprints in the processing of ginseng materials to produce drugs which qualify as pharmaceutical grade compns. which are suitable for use in clin. or veterinary settings to **treat** and/or ameliorate diseases, disorders or conditions. Development of a biol. and chem. PharmaPrint .RTM. of ginseng is provided. Results of bioassays and chem. anal. of ginseng is also presented.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 49 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 130:306599 CA
TI Antisense oligonucleotides capable of binding to multiple targets and their use in the **treatment** of respiratory disease
IN Nyce, Jonathan W.
PA East Carolina University, USA
SO PCT Int. Appl., 120 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9913886	A1	19990325	WO 1998-US19419	19980917
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2003087845	A1	20030508	US 1998-93972	19980609
CA 2304312	AA	19990325	CA 1998-2304312	19980917
AU 9893951	A1	19990405	AU 1998-93951	19980917
AU 752531	B2	20020919		
EP 1019065	A1	20000719	EP 1998-947089	19980917
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
BR 9812650	A	20000822	BR 1998-12650	19980917
JP 2003517428	T2	20030527	JP 2000-511506	19980917
PRAI US 1997-59160P	P	19970917		
US 1998-93972	A	19980609		
WO 1998-US19419	W	19980917		

AB Antisense oligonucleotides carrying sequences that will allow them to bind to more than one mRNA in a target cell are described. Such oligonucleotides can be used as a single **treatment** for diseases having more than one contributing pathway. In particular, oligonucleotides effective against genes involved in the etiol. of respiratory disease are targeted. Preferably, the oligonucleotides are low in adenosine (.ltoreq.15%) and may have adenosines substituted with analogs. These oligonucleotides are targeted to high (G+C) sequences within mRNAs. Thus, phosphorothioate antisense oligonucleotide (HAdA1AS, 5'-gatggagggcggcatggcggg-3') designed for the adenosine A1 receptor is provided. HAdA1AS significantly and specifically reduces the in vivo response to adenosine challenge in a dose-dependent manner, is effective in protection against aeroallergen-induced bronchoconstriction (house dust mite), has an unexpected long-term duration of effect (8.3 days for both PC50 adenosine and resistance), and is free of side effects that might be toxic to the recipient. Such oligonucleotides may be used for **treating** a disease or condition assocd. with lung airway, such as bronchoconstriction, **inflammation**, or allergies.
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 50 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 130:276651 CA
TI Morphine tolerance in arthritic rats and serotonergic system
AU Li, Jihn-Yih; Wong, Chung-Hang; Huang, Kuo-Sheng; Liang, Kai-Wen; Lin, Ming-Yu; Tan, Peter PC; Chen, Jin-Chung
CS Department of Anesthesiology, Chung-Gung Memorial Hospital, Tao-Yuan, 333, Taiwan
SO Life Sciences (1999), 64(10), PL111-PL116
CODEN: LIFSAK; ISSN: 0024-3205
PB Elsevier Science Inc.
DT Journal
LA English

AB To understand whether chronic **inflammation** alters the development of morphine tolerance, the tail-flick test was used to evaluate the analgesic effect of morphine (75 mg tablet, s.c.) in the arthritic rats at the day 9-12 after the inoculation with Freund's adjuvant. Spinal cord monoamines and amino acid neurotransmitters were concomitantly measured. Chronic **inflammation** attenuated the antinociceptive effect of morphine as tolerance developed faster in the arthritic rats compared to the vehicle-**treated** controls. In addn., ratio of 5-hydroxyindole-3-acetic acid/ 5-hydroxytryptamine (5-HIAA/5-HT) increased in the lumbar spinal cord of arthritic rats without any change in the concns. of norepinephrine, glutamate, aspartate or **GABA**. Interestingly, increased serotonin turnover in the spinal cord was obsd. in both control and arthritic rats 24 h after morphine **treatment**. Overall, the results suggest a significant role of serotonin up-regulation in the spinal cord during chronic pain and the development of morphine tolerance.
RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 51 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 130:205539 CA
TI Method and compositions for promoting the neural synthesis and release of neurotransmitters using neurotransmitter precursors in combination with xanthines
IN Shell, William E.; Jarmel, Mark E.
PA Nicada, Inc., USA
SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9908681	A1	19990225	WO 1998-US16882	19980813
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9891975	A1	19990308	AU 1998-91975	19980813
PRAI	US 1997-55732P	P	19970813		
	US 1998-133660	A	19980812		
	WO 1998-US16882	W	19980813		

AB A method and compns. for promoting the neural synthesis and release in an animal subject of the neurotransmitters acetylcholine, **GABA**, glutamate, norepinephrine, dopamine, aspartate, histamine and serotonin. To enhance release of the neurotransmitter in the subject precursors for each of these neurotransmitters may be administered concomitantly with a xanthine and with one or more precursors for another neurotransmitter selected from precursors for the neurotransmitters histamine, glutamine and aspartate. The xanthines include caffeine, theophylline and theobromine. This procedure for the promotion of synthesis and release of the neurotransmitters may be employed in the **treatment** of subjects having a neurotransmitter deficiency, including reduced neural tone and excessive neural activity. The compns. of the invention promote the synthesis and release of specific neurotransmitters while avoiding the side effects seen with other pharmaceutical agents.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 52 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 130:191891 CA
TI **GABA** analogs to prevent and **treat** gastrointestinal damage and ethanol withdrawal syndrome
IN Guglietta, Antonio; Taylor, Charles, Price, Jr.; Ren, Jiayuan; Watson, W. P.; Rafferty, Michael Francis; Diop, Laurent; Chovet, Maria; Bueno,

Lionel; Little, Hilary J.
PA Warner-Lambert Company, USA; The University of Oklahoma
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9908671	A1	19990225	WO 1998-US17082	19980818
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9892930	A1	19990308	AU 1998-92930	19980818
	EP 1009399	A1	20000621	EP 1998-945758	19980818
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	BR 9812133	A	20000718	BR 1998-12133	19980818
	JP 2001515033	T2	20010918	JP 2000-509411	19980818
	CA 2297163	C	20011120	CA 1998-2297163	19980818
	NZ 502729	A	20021025	NZ 1998-502729	19980818
	ZA 9807493	A	19990707	ZA 1998-7493	19980819
	US 6127418	A	20001003	US 1999-284710	19990419
	MX 200001093	A	20001020	MX 2000-1093	20000131
	NO 2000000786	A	20000217	NO 2000-786	20000217
	US 6242488	B1	20010605	US 2000-567191	20000509
	US 2001014698	A1	20010816	US 2001-804742	20010313
	US 6426368	B2	20020730		
PRAI	US 1997-56753P	P	19970820		
	US 1998-74794P	P	19980216		
	US 1998-82936P	P	19980424		
	WO 1998-US17082	W	19980818		
	US 1999-284710	A3	19990419		
	US 2000-567191	A3	20000509		

OS MARPAT 130:191891
AB **GABA** analogs are useful to prevent and **treat** gastrointestinal damage and ethanol withdrawal syndrome. Preferred **treatments** employ gabapentin or pregabalin.
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 53 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 130:191890 CA
TI **GABA** analogs to prevent and **treat** gastrointestinal damage and ethanol withdrawal syndrome
IN Guglietta, Antonio; Taylor, Charles Price, Jr.; Ren, Jiayuan; Watson, W. P.; Rafferty, Michael Francis; Diop, Laurent; Chovet, Maria; Bueno, Lionel; Little, Hilary J.
PA Warner-Lambert Company, USA; The University of Oklahoma; Taylor, Charles Price, Jr.; et al.
SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9908670	A1	19990225	WO 1998-US15694	19980729
	W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

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     AU 9886685         A1   19990308       AU 1998-86685    19980729
     ZA 9807493         A    19990707       ZA 1998-7493     19980819
     US 6242488         B1   20010605       US 2000-567191   20000509
PRAI US 1997-56753P     P    19970820
     US 1998-74794P     P    19980216
     US 1998-82936P     P    19980424
     WO 1998-US15694    W    19980424
     US 1999-284710     A3   19990419
OS   MARPAT 130:191890
AB   GABA analogs are useful to prevent and treat
     gastrointestinal damage and ethanol withdrawal syndrome.  Preferred
     treatments employ gabapentin or pregabalin.
RE.CNT  5      THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6   ANSWER 54 OF 75  CA  COPYRIGHT 2003 ACS on STN
AN   130:90504  CA
TI   Use of GABA analogs such as gabapentin in the manufacture of a
     medicament for treating inflammatory diseases
IN   Schrier, Denis; Taylor, Charles Price, Jr.; Westlund-High, Karin Nanette
PA   Warner-Lambert Company, USA; Board of Regents of the University of Texas
     System
SO   PCT Int. Appl., 35 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE           APPLICATION NO.  DATE
     ---------------    ----  --------       ---------------  --------
PI   WO 9858641          A1   19981230       WO 1998-US13107  19980624
         W:  AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GW, HU, ID, IL, IS,
             JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG,
             SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD,
             RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
             FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
             CM, GA, GN, ML, MR, NE, SN, TD, TG
     AU 9883758          A1   19990104       AU 1998-83758    19980624
     AU 735675           B2   20010712
     ZA 9805517          A    19990120       ZA 1998-5517     19980624
     EP 994704           A1   20000426       EP 1998-934170   19980624
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
     BR 9812265          A    20000718       BR 1998-12265    19980624
     JP 2002506449       T2   20020226       JP 1999-505021   19980624
     NZ 501626           A    20020328       NZ 1998-501626   19980624
     US 6329429          B1   20011211       US 1999-403867   19991025
     MX 9909996          A    20000331       MX 1999-9996     19991029
     NO 9906468          A    20000221       NO 1999-6468     19991223
     US 2002032235       A1   20020314       US 2001-924656   20010808
PRAI US 1997-50736P      P    19970625
     US 1998-84183P      P    19980504
     WO 1998-US13107     W    19980624
     US 1999-403867      A3   19991025
OS   MARPAT 130:90504
AB   GABA analogs, e.g. gabapentin and pregabalin, are useful for the
     prevention and treatment of inflammatory diseases.
RE.CNT  5      THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6   ANSWER 55 OF 75  CA  COPYRIGHT 2003 ACS on STN
AN   129:298385  CA
TI   Use of .gamma.-aminobutyric acid as stimulant of interleukin formation
IN   Laves, Hans-Georg
PA   Laves-Arzneimittel G.m.b.H. und Co. Verwaltungs K.-G., Germany
SO   Ger. Offen., 6 pp.
     CODEN: GWXXBX
DT   Patent
LA   German
```

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19712633	A1	19981008	DE 1997-19712633	19970326
PRAI	DE 1997-19712633		19970326		

AB Administration of **GABA** stimulates formation of interleukins, esp. of IL-6, and is useful for stimulation of the immune system and **treatment** of **inflammatory** disorders, esp. when combined with low concns. of lipopolysaccharide. **GABA** may be administered i.v. or s.c. as a soln. contg. 1-1000 .mu.g/kg/day; administration as tablets, capsules, or topically is also possible. Thus, **GABA** and **GABA**-contg. exts. of Escherichia coli stimulated human mononuclear cells to form IL-6, as shown by the activity of supernatants from stimulated mononuclear cells in increasing the incorporation of radioactive thymidine into IL-6-dependent murine B-cell line 7TD1. A procedure for purifn. of **GABA** from an E. coli ext. is presented.

RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 56 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 128:226257 CA
TI Compositions and methods modulating amyloid precursor protein for **treatment** of neurological disorders and neurodegenerative diseases, including Alzheimer's disease
IN Lee, Robert K. K.; Wurtman, Richard J.
PA Massachusetts Institute of Technology, USA
SO PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DT Patent
LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9809523	A1	19980312	WO 1997-US15321	19970905
	W: CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 1006798	A1	20000614	EP 1997-941386	19970905
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI	US 1996-25507P	P	19960905		
	US 1997-33765P	P	19970115		
	WO 1997-US15321	W	19970905		

AB It has been discovered that the stimulation of .beta.-adrenergic receptors, which activate cAMP formation, give rise to increased APP and GFAP synthesis in astrocytes. Hence, the in vitro or in vivo exposure of neuronal cells to certain compns. comprising .beta.-adrenergic receptor ligands or agonists, including, e.g., norepinephrine, isoproterenol and the like, increases APP mRNA transcription and consequent APP overprodn. These increases are blocked by .beta.-adrenergic receptor antagonists, such as propranolol. The in vitro or in vivo **treatment** of these cells with 8Br-cAMP, prostaglandin E2 (PG E2), forskolin, and nicotine ditartrate also increased APP synthesis, including an increase in mRNA and holoprotein levels, as well as an increase in the expression of glial fibrillary acidic protein (GFAP). Compns. and methods are disclosed of regulating APP overexpression and mediating reactive astrogliosis through cAMP signaling or the activation of .beta.-adrenergic receptors. It has further been found that the increase in APP synthesis caused by 8Br-cAMP, PG E2, forskolin, or nicotine ditartrate is inhibited by immunosuppressants or anti-**inflammatory** agents, such as cyclosporin A, and FK-506 (tacrolimus), as well as ion-channel modulators, including ion chelating agents such as EGTA, or calcium/calmodulin kinase inhibitors, such as KN93. The present invention has broad implications in the alleviation, **treatment**, or prevention of neurol. disorders and neurodegenerative diseases, including Alzheimer's disease.

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 57 OF 75 CA COPYRIGHT 2003 ACS on STN

AN 128:149590 CA
TI Isobutyl-**GABA** and its derivatives for the **treatment** of pain
IN Singh, Lakhbir
PA Warner-Lambert Co., USA; Singh, Lakhbir
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9803167	A1	19980129	WO 1997-US12390	19970716
W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, HU, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9736024	A1	19980210	AU 1997-36024	19970716
AU 714980	B2	20000113		
CN 1223574	A	19990721	CN 1997-196041	19970716
CN 1094757	B	20021127		
EP 934061	A1	19990811	EP 1997-932617	19970716
EP 934061	B1	20030528		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9710536	A	19990817	BR 1997-10536	19970716
NZ 332762	A	20000929	NZ 1997-332762	19970716
JP 2000515149	T2	20001114	JP 1998-507062	19970716
IL 126999	A1	20020310	IL 1997-126999	19970716
AT 241351	E	20030615	AT 1997-932617	19970716
ZA 9706562	A	19980203	ZA 1997-6562	19970723
US 6001876	A	19991214	US 1998-43358	19980715
NO 9900279	A	19990122	NO 1999-279	19990122
PRAI US 1996-22337P	P	19960724		
WO 1997-US12390	W	19970716		

OS MARPAT 128:149590
AB A method is provided for using certain analogs of glutamic acid and .gamma.-aminobutyric acid in pain therapy.
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 58 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 126:180834 CA
TI Evidence that a hybrid molecule of norfloxacin and biphenylacetic acid is a potent antagonist at the GABAA receptor antagonist
AU Imanishi, T.; Akahane, K.; Akaike, N.
CS Department of Physiology, Kyushu University Faculty of Medicine, Fukuoka, 812-82, Japan
SO Neuropharmacology (1996), 35(9/10), 1271-1277
CODEN: NEPHBW; ISSN: 0028-3908
PB Elsevier
DT Journal
LA English
AB The combination of some fluorinated quinolone antimicrobials and certain non-steroidal anti-**inflammatory** drugs (NSAIDs), such as fenbufen, has been reported to elicit serious convulsions in humans. Fluoroquinolones, including norfloxacin (NFLX) and NSAIDs synergistically inhibit GABAA receptors. The mechanism(s) of the synergism, however, at present remains unclear. In the present study, the hypothesis that NFLX and biphenylacetic acid (BPA), an active metabolite of fenbufen, undergo an intermol. interaction to produce a more potent GABAA antagonist, was investigated by examg. the effects of two hybrid mols. of NFLX linked with BPA on **GABA**-evoked whole cell currents, recorded from rat hippocampal neurons using the perforated-patch clamp technique. Hybrid-1, with a -CONH(CH2)3- chain between NFLX and BPA, inhibited the **GABA** response more potently than co-**treatment** with NFLX and BPA. In

contrast, hybrid-2 with a -CONH- chain between NFLX and BPA, exhibited only weak inhibition of the **GABA** response. The characterization of the inhibition of the **GABA** response in the presence of hybrid-1 was similar to that of the combination of NFLX and BPA regarding the following: (1) there was a rightward parallel shift of the concn.-response curve of **GABA** at lower concns. and a suppression of the maximal response to **GABA** at higher concns.; (2) it was voltage-independent; and (3) there was no influence on the reversal potential of the **GABA** response. These results therefore suggest that NFLX and BPA interact with the GABAA receptor at nearby sites and thus suppress the **GABA** response.

L6 ANSWER 59 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 125:48384 CA
TI Convulsant effects of NM441, a prodrug type antibacterial agent of the quinolone class
AU Ukai, Yojiro; Yamazaki, Akira; Kurosaka, Chiemi; Ishima, Tsuyoshi; Yoshikuni, Yoshiaki; Kimura, Kiyoshi
CS Res. Lab., Nippon Shinyaku Co., Ltd., Kyoto, 601, Japan
SO Nippon Kagaku Ryoho Gakkai Zasshi (1996), 44(Suppl. 1), 102-12
CODEN: NKRZE5; ISSN: 1340-7007
DT Journal
LA Japanese
AB Convulsant effects of NM441 were compared with those of ofloxacin (OFLX), ciprofloxacin (CPFX), lomefloxacin (LFLX) and enoxacin (ENX). These quinolones caused no convulsion in mice when orally **treated** alone, however, they elicited clonic and tonic convulsions and death by the combined **treatment** with fenbufen. The order of potency of their convulsant activity was ENX > LFLX > NM441 > CPFX > OFLX. NM441 as well as other quinolones caused convulsions and death by the combined oral **treatment** with theophylline in the order of potency: LFLX .gtoreq. OFLX .gtoreq. ENX > NM441 > CPFX. NM441 alone showed no potentiation of convulsant activities of bicuculline, pentetrazol and maximal electroshock. The i.v. injection of NM394, an active metabolite of NM441, generated spike activities or seizure discharges from the thalamus and cerebral cortex in rabbits, and its effect was less significant than that of ENX and CPFX. Oral administration of NM441 showed no changes in the behavior and EEGs in rabbits. Spinal reflex potentials in cats were not affected by i.v. or oral **treatments** with NM394 or NM441, resp. Binding of [3H] muscimol to the membrane prepns. from rat brains was weakly inhibited by NM394 alone, and the inhibition was markedly potentiated in the presence of biphenylacetic acid, an active metabolite of fenbufen. The interaction of NM394 with GABAA receptors may partly contribute to the convulsions caused by NM441.

L6 ANSWER 60 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 124:45619 CA
TI Attenuation by valproate of c-fos immunoreactivity in trigeminal nucleus caudalis induced by intracisternal capsaicin
AU Cutrer, F. Michael; Limmroth, Volker; Ayata, Gamze; Moskowitz, Michael A.
CS Dep. Neurology, Massachusetts General Hospital, Charlestown, MA, 02129, USA
SO British Journal of Pharmacology (1995), 116(8), 3199-204
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton
DT Journal
LA English
AB Valproic acid, useful in the **treatment** of migraine, is an inhibitor of .gamma.-aminobutyric acid (**GABA**) aminotransferase and activator of glutamic acid decarboxylase. Its mechanism in migraine remains obscure. The effects of valproic acid (2-propylpentanoic acid) were examd. on the no. of cells expressing c-fos-like immunoreactivity (c-fos-LI), a marker of neuronal activation, within the trigeminal nucleus caudalis (lamina, I, IIo; TNC) 2 h after intracisternal injection of the irritant, capsaicin (0.1 mL; 15.25 .mu.g mL-1), in urethane-anesthetized Hartley guinea-pigs. Pos. cells were counted in eighteen sections (50 .mu.m) at three representative levels (rostral, middle and caudal) within lamina I, IIo of the TNC in 90 animals. Numerous cells were labeled after capsaicin instillation (244 .+-. 25; 1 mL; 15.25 mM) but not after

capsaicin vehicle (11 .+-. 1). Pos. cells were also found within the medial reticular nucleus, the area postrema and the nucleus of the solitary intact. A similar distribution has been demonstrated previously after application of intracisternal irritants such as autologous blood or carrageenin. Valproate (.gtoreq.10 mg kg-1, i.p.) reduced labeled cells by 52% (P <0.05) in lamina I, IIo but not within the area postrema, the nucleus of the solitary tract or the medial reticular nucleus. A similar finding was obtained previously after administration of sumatriptan, dihydroergotamine or the NK1 receptor antagonist RPR 100893. Pretreatment with bicuculline (30 .mu.g kg-1; i.p.), a GABAA antagonist, but not phaclofen (1 mg kg-1) a GABAB antagonist, reversed the effect of valproate and increased c-fos pos. cells within lamina I, IIo. Somewhat paradoxically, bicuculline by itself (30 .mu.g kg-1 i.p.) decreased the no. of labeled cells suggesting that more than a single GABAergic mechanism can suppress c-fos expression. We conclude that the mechanism of action of valproate is mediated via GABAA receptors. Since valproate decreases both c-fos expression and as previously shown, neurogenic **inflammation** within the meninges, the GABAA receptor complex might provide an important target for drug development in migraine and related headaches.

L6 ANSWER 61 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 123:188441 CA
TI Peripheral GABAA receptor-mediated effects of sodium valproate on dural plasma protein extravasation to substance P and trigeminal stimulation
AU Lee, Won Suk; Limmroth, Volker; Ayata, Cenk; Cutrer, F. Michael; Waeber, Christian; Yu, Xianjie; Moskowitz, Michael A.
CS Massachusetts General Hospital, Charlestown, MA, 02129, USA
SO British Journal of Pharmacology (1995), 116(1), 1661-7
CODEN: BJPCBM; ISSN: 0007-1188
PB Macmillan Scientific & Medical Division
DT Journal
LA English
AB The **GABA** transaminase inhibitor and activator of glutamic acid decarboxylase, valproic acid is being used for the **treatment** of migraine. Its mechanism of action is unknown. The authors tested the effects of sodium valproate and GABAA-agonist muscimol on dural plasma protein ([125I]-bovine serum albumin) extravasation evoked by either unilateral trigeminal ganglion stimulation (0.6 mA, 5 ms, 5 Hz, 5 min) or substance P (SP) administration (1 nmol kg-1, i.v.) in anesthetized Sprague-Dawley rats. I.p. injection of sodium valproate or muscimol, but not baclofen (.ltoreq.10 mg kg-1, i.p.) dose-dependently reduced dural plasma protein extravasation caused either by elec. trigeminal stimulation (ED50: 6.6 .+-. 1.4 mg kg-1, i.p., and 58 .+-. 18 .mu.g, i.p. for valproate or muscimol, resp.) or by i.v. subtance P administration (ED50: 3.2 .+-. 1.4 mg kg-1, i.p. and 385 .+-. 190 .mu.g kg-1, i.p. for valproate or muscimol, resp.). Valproate (6.6 mg kg-1, i.p.) or muscimol (58 .mu.g kg-1, i.p.) had no effect on mean arterial blood pressure or heart rate when measured for 30 min after i.p. administration. The GABAA-antagonist bicuculline (0.01 mg kg-1, i.p.) completely reversed the effect of valproate and muscimol on plasma extravasation following elec. stimulation or substance P administration, whereas the GABAB-receptor antagonist, phaclofen (0.01-1 mg kg-1, i.p.) did not. Bicuculline or phaclofen, given alone, did not alter the plasma extravasation response after either elec. stimulation or SP administration. Valproate decreased plasma extravasation following substance P administration in adult animals, neonatally **treated** with capsaicin by a bicuculline-reversible mechanism. This suggests that GABAA-receptors are not found primarily on those afferent neurons or fibers which are sensitive to capsaicin **treatment** in neonatal rats. In conclusion, sodium valproate blocks plasma extravasation in the meninges through GABAA-mediated postjunctional receptors probably within the meninges. The dosages required are comparable to those used clin. Agonists and modulators at the GABAA receptor may become useful for the development of selective therapeutic agents for migraine and cluster headache.

L6 ANSWER 62 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 122:29393 CA
TI Spinal cord SP release and hyperalgesia in monoarthritic rats: involvement

of the GABAB receptor system
AU Malcangio, Marzia; Bowery, Norman G.
CS Dept. Pharmacology, School of Pharmacy, London, WC1N 1AX, UK
SO British Journal of Pharmacology (1994), 113(4), 1561-6
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton
DT Journal
LA English
AB Monoarthritis was induced in Lewis rats by interdermal injection in the left hind paw of a suspension of Mycobacterium tuberculosis in mineral oil (500 .mu.g 100 .mu.L-1). Controls were injected with 100 .mu.L mineral oil. Withdrawal latencies to thermal stimuli of the **inflamed** paw, the contralateral and both paws of control rats were measured at daily intervals after injection of the plantar test. After detection of the pain threshold, rat spinal cords were removed and horizontal dorsal slices were mounted in a 3-compartment bath to measure elec.-evoked release of substance P-like immunoreactivity (SP-LI). The **inflamed** paw of monoarthritic rats exhibited a lower pain threshold to thermal stimuli than the contralateral paw of the same animals and both paws of control rats. **Inflamed** paw hyperalgesia was maximal 2 days after injection, and declined gradually between 7 to 21 days with no evidence of excitability of withdrawal reflexes after 28 days. During the 28 days study, monoarthritis rats gained less wt. than control rats. Elec. stimulation of the dorsal roots attached to rat isolated spinal cord slices induced a significant increase (174 .+-. 18% of basal outflow which was 30.3 fmol 8 mL-1, n = 5) in SP-LI release. One-week after induction of **inflammation** no differences in the amt. of SP-LI released from the spinal cord of incomplete Freund's adjuvant-**treated** rats (IFA) and Freund's adjuvant-**treated** rats (CFA) were detected. Two weeks after, CFA spinal cord tended to release more SP-LI than IFA cords and, 21 days after injection, the spinal cord of CFA rats released significantly more peptide than IFA rats (17.8 .+-. 2.8 fmol mL-1, n = 12 and 6.9 .+-. 3.2 fmol mL-1, n = 9, resp.). Twenty-one days after **treatment**, the evoked release from monoarthritic rat spinal cords was increased by 263 .+-. 42% (n = 3) in the presence of the GABAB receptor antagonist, CGP 36742 (100 .mu.M) which also significantly potentiated monoarthritis-induced hyperalgesia up to 45 min after injection (100 mg kg-1, i.p.). These findings may provide a basis for a novel approach to chronic pain therapy but also an explanation for the lack of analgesia produced by the GABAB agonist, baclofen, in chronic as compared to acute pain.

L6 ANSWER 63 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 121:252981 CA
TI Expression of GAD mRNA in spinal cord neurons of normal and monoarthritic rats
AU Castro-Lopes, J. M.; Toelle, T. R.; Pan, B.; Zieglgaensberger, W.
CS Institute of Histology and Embryology, Faculty of Medicine of Oporto, Porto, 4200, Port.
SO Molecular Brain Research (1994), 26(1-2), 169-76
CODEN: MBREE4; ISSN: 0169-328X
DT Journal
LA English
AB This study was carried out to investigate whether the increase of **GABA** levels in spinal cord dorsal horn in response to chronic **inflammatory** lesions results from an enhanced expression of the gene that governs the prodn. of glutamate decarboxylase (GAD), the enzyme responsible for **GABA** synthesis. In situ hybridization was used to visualize neurons expressing GAD mRNA within the spinal cord, in both intact rats and in animals bearing chronic monoarthritis induced by intraarticular injection of complete Freund's adjuvant. In control normal animals, neuronal labeling by an antisense oligonucleotide probe occurred throughout the spinal gray matter, except in the motoneuronal pool of Rexed's lamina IX. In **treated** animals 4 days after the induction of monoarthritis, a significant increase in the no. of labeled cells occurred in the superficial laminae (25.3%) and the neck (17.2%) of the ipsilateral dorsal horn at segments L4-L5 which contain the projection domain of the ankle joint. At 2 wk, values were, resp., 20.2% and 13.9% over contralateral values, and an increase of 12.4% was found in the

ventral horn. At 3 wk, the ipsilateral increase of labeled cells was restricted to the superficial dorsal horn (15.2%). These findings emphasize the role played by the spinal GABAergic system in the modulation of chronic nociceptive input. It is suggested that the response of the spinal GABAergic system depends on the activation of GAD gene transcription in spinal neurons.

L6 ANSWER 64 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 121:99126 CA
TI Mechanism of quinolone-induced convulsion and anticonvulsant effect of barbiturate for this seizure
AU Kanemitsu, Keiji
CS Dep. Intern. Med. and Lab. Med., St. Marianna Univ. Sch. Med., Kawasaki, 216, Japan
SO Sei Marianna Ika Daigaku Zasshi (1993), 21(6), 1177-85
CODEN: SMIZDS; ISSN: 0387-2289
DT Journal
LA Japanese
AB In recent years, many new quinolones have been synthesized and used for the **treatment** of infectious diseases. Quinolone-induced convulsion, however, was reported as side effects in the central nervous system (CNS), esp. in concurrent use with non-steroidal anti-**inflammatory** drugs (NSAIDs). In order to elucidate this mechanism, the authors studied the convulsive effect of enoxacin (ENX), norfloxacin (NFLX), ciprofloxacin (CPFX), and lomefloxacin (LFLX) by injection into the lateral ventricle of mice with or without NSAIDs. The authors also studied the effect of ENX, NFLX, CPFX, and LFLX on receptor binding of .gamma.-aminobutyric acid (**GABA**), an inhibitory transmitter in CNS, with or without NSAIDs. Intraventricular injection of quinolones induced convulsions in mice in a dose dependent-manner. The convulsive activity of quinolones was enhanced by concurrent administration with NSAIDs. The quinolones used in this study inhibited **GABA** receptor binding in a concn.-dependent manner and this inhibitory activity was enhanced in the presence of NSAIDs except acetylsalicylic acid. Furthermore, a correlation was obtained between ED50 values and IC50 values. The authors studied the effect of barbiturate on enoxacin-induced convulsion. Pentobarbital sodium decreased the convulsive activity of ENX with or without biphenylacetic acid (BPA). These results suggest that quinolones induce convulsions through the inhibition of **GABA** receptor binding.

L6 ANSWER 65 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 120:295917 CA
TI Carrageenan-induced **inflammation** of the hind foot provokes a rise of **GABA**-immunoreactive cells in the rat spinal cord that is prevented by peripheral neurectomy or neonatal capsaicin **treatment**
AU Castro-Lopes, J.M.; Tavares, I.; Tolle, T.R.; Coimbra, A.
CS Inst. Histol. and Embryol., Fac. Med. Oporto, Porto, 4200, Port.
SO Pain (1994), 56(2), 193-201
CODEN: PAINDB; ISSN: 0304-3959
DT Journal
LA English
AB An increase in the no. of .gamma.-aminobutyric acid (**GABA**)-immunoreactive cells is reported in the superficial dorsal horn of the rat spinal cord upon unilateral **inflammation** of the hind foot caused by s.c. carrageenan injection. The rise of GABAergic cells was restricted to the ipsilateral dorsal horn, reaching a peak value of 23.4% over the contralateral side 4 days after carrageenan injection. Sciatic neurectomy or neonatal capsaicin **treatment** prevented this effect. These findings suggest that dorsal horn **GABA** is up-regulated by the increase of noxious inflow conveyed by unmyelinated C fibers from the **inflamed** tissues.

L6 ANSWER 66 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 120:253358 CA
TI Cyclodextrin complexes with polymers, drugs, agrochemicals and cosmetics
IN Loftsson, Thorsteinn
PA Iceland
SO Eur. Pat. Appl., 46 pp.

CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 579435	A1	19940119	EP 1993-305280	19930706
	EP 579435	B1	19990317		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	US 5324718	A	19940628	US 1992-912853	19920714
	AT 177647	E	19990415	AT 1993-305280	19930706
	ES 2132190	T3	19990816	ES 1993-305280	19930706
	US 5472954	A	19951205	US 1994-240510	19940511
PRAI	US 1992-912853		19920714		
	EP 1993-305280		19930706		

AB A method for enhancing the complexation of a cyclodextrin (I) with a lipophilic and/or water-labile drug, comprising combining .apprx.0.1-70% (wt./vol.) of I and .apprx.0.001-5% (wt./vol.) of a water-sol. polymer in an aq. medium. The polymer and I are dissolved in the aq. medium before the drug is added. To a soln. contg. Na CM-cellulose 0.25 and 2-hydroxypropyl-.beta.-cyclodextrin 10% was added acetazolamide (II) and the soln. was heated at 120.degree. for 20 min and allowed to equilibrate at room temp. for 3 days and amt. of II was detd. The soly. of II was 3.11mg/mL as compared to 0.7 for control contg. only II. Different formulations contg. cyclodextrin complexes with polymers and drugs are disclosed.

L6 ANSWER 67 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 120:226984 CA
TI Compositions of oral nondissolvable matrixes for transmucosal administration of medicaments
IN Stanley, Theodore H.; Hague, Brian
PA University of Utah Research Foundation, USA
SO U.S., 20 pp. Cont.-in-part of U.S. 4,863,737.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 9

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5288498	A	19940222	US 1989-403752	19890905
	US 4671953	A	19870609	US 1985-729301	19850501
	EP 487520	A1	19920603	EP 1989-909497	19890816
	EP 487520	B1	19950412		
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
	JP 05501539	T2	19930325	JP 1989-504878	19890816
	JP 2801050	B2	19980921		
	AU 641127	B2	19930916	AU 1989-40704	19890816
	AT 120953	E	19950415	AT 1989-909497	19890816
	CA 1338978	A1	19970311	CA 1989-609378	19890824
	AU 9050352	A1	19910408	AU 1990-50352	19890905
	AU 645966	B2	19940203		
	EP 493380	A1	19920708	EP 1990-902584	19890905
	EP 493380	B1	19971029		
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
	US 5132114	A	19920721	US 1989-402881	19890905
	JP 05501854	T2	19930408	JP 1990-502779	19890905
	CA 1339075	A1	19970729	CA 1989-610329	19890905
	AT 159658	E	19971115	AT 1990-902584	19890905
	WO 9103236	A1	19910321	WO 1990-US4369	19900803
	W: AU, CA, JP, NO				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
	AU 9063371	A1	19910408	AU 1990-63371	19900803
	AU 642664	B2	19931028		
	EP 490944	A1	19920624	EP 1990-913359	19900803
	EP 490944	B1	19960529		
	R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
	JP 05500058	T2	19930114	JP 1990-512483	19900803
	JP 2749198	B2	19980513		

	AT 138562	E	19960615	AT 1990-913359	19900803
	ES 2089027	T3	19961001	ES 1990-913359	19900803
	CA 2066403	C	19980414	CA 1990-2066403	19900803
	NO 9200565	A	19920213	NO 1992-565	19920213
	DK 9200193	A	19920214	DK 1992-193	19920214
	NO 9200858	A	19920304	NO 1992-858	19920304
	NO 9200855	A	19920410	NO 1992-855	19920304
	NO 9200854	A	19920427	NO 1992-854	19920304
	DK 9200300	A	19920505	DK 1992-300	19920305
	AU 9460697	A1	19940623	AU 1994-60697	19940427
	US 5855908	A	19990105	US 1994-339655	19941115
PRAI	US 1985-729301	A2	19850501		
	US 1987-60045	A2	19870608		
	EP 1989-909497	A	19890816		
	WO 1989-US3518	W	19890816		
	US 1989-403752	A	19890905		
	WO 1989-US3801	A	19890905		
	WO 1990-US4369	A	19900803		
	US 1993-152414	B1	19931112		

AB Compns. and methods of manuf. for producting a medicament compn. capable of absorption through the mucosal tissues of the mouth, pharynx, and esophagus are disclosed. The present invention relates to such compns. and methods which are useful in administering lipophilic and nonlipophilic drugs in a dose-to-effect manner such that sufficient drug is administered to produce precisely a desired effect. The invention also relates to manufg. techniques that enable therapeutic agents to be incorporated into nondissolvable drug containment matrixes which are capable of releasing the drug within a patient's mouth. An appliance or holder is preferably attached to the drug containment matrix. Employing the present invention the drug may be introduced into the patient's bloodstream almost as fast as through injection, and much faster than using the oral administration route, while avoiding the neg. aspects of both of these methods. The nondissolvable drug containment matrix may include permeation enhancers to increase the drug adsorption by the mucosal tissues of the mouth. The matrix compn. may also include pH buffering agents to modify the saliva pH thereby increasing the absorption of the drug through the mucosal tissues. Figures show views of some dosage forms.

L6 ANSWER 68 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 120:226981 CA
TI Compositions of oral dissolvable medicaments
IN Stanley, Theodore H.; Hague, Brian
PA University of Utah, USA
SO U.S., 22 pp. Cont.-in-part of U.S. 4,863,737.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 9

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5288497	A	19940222	US 1989-403751	19890905
	US 4671953	A	19870609	US 1985-729301	19850501
	EP 487520	A1	19920603	EP 1989-909497	19890816
	EP 487520	B1	19950412		
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
	JP 05501539	T2	19930325	JP 1989-504878	19890816
	JP 2801050	B2	19980921		
	AU 641127	B2	19930916	AU 1989-40704	19890816
	AT 120953	E	19950415	AT 1989-909497	19890816
	CA 1338978	A1	19970311	CA 1989-609378	19890824
	AU 9050352	A1	19910408	AU 1990-50352	19890905
	AU 645966	B2	19940203		
	EP 493380	A1	19920708	EP 1990-902584	19890905
	EP 493380	B1	19971029		
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
	US 5132114	A	19920721	US 1989-402881	19890905
	JP 05501854	T2	19930408	JP 1990-502779	19890905
	CA 1339075	A1	19970729	CA 1989-610329	19890905
	AT 159658	E	19971115	AT 1990-902584	19890905

	WO 9103237	A1	19910321	WO 1990-US4384	19900803
	W: AU, CA, JP, NO				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
	AU 9062877	A1	19910408	AU 1990-62877	19900803
	AU 645265	B2	19940113		
	EP 490916	A1	19920624	EP 1990-912733	19900803
	EP 490916	B1	19951018		
	R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
	JP 05503917	T2	19930624	JP 1990-512229	19900803
	EP 630647	A1	19941228	EP 1994-111352	19900803
	EP 630647	B1	19990303		
	R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
	AT 129148	E	19951115	AT 1990-912733	19900803
	ES 2077686	T3	19951201	ES 1990-912733	19900803
	CA 2066423	C	19980414	CA 1990-2066423	19900803
	AT 177007	E	19990315	AT 1994-111352	19900803
	ES 2133448	T3	19990916	ES 1994-111352	19900803
	NO 9200565	A	19920213	NO 1992-565	19920213
	DK 9200193	A	19920214	DK 1992-193	19920214
	NO 9200857	A	19920406	NO 1992-857	19920304
	NO 9200855	A	19920410	NO 1992-855	19920304
	NO 9200854	A	19920427	NO 1992-854	19920304
	DK 9200300	A	19920505	DK 1992-300	19920305
	AU 9455218	A1	19940428	AU 1994-55218	19940218
	AU 668004	B2	19960418		
	AU 9460697	A1	19940623	AU 1994-60697	19940427
	US 5824334	A	19981020	US 1996-636828	19960419
	US 5783207	A	19980721	US 1997-795359	19970204
	US 5785989	A	19980728	US 1997-822560	19970319
PRAI	US 1985-729301	A2	19850501		
	US 1987-60045	A2	19870608		
	EP 1989-909497	A	19890816		
	WO 1989-US3518	W	19890816		
	US 1989-403751	A	19890905		
	WO 1989-US3801	A	19890905		
	EP 1990-912733	A3	19900803		
	WO 1990-US4384	A	19900803		
	US 1993-152396	B1	19931112		
	US 1994-333233	B2	19941102		
	US 1995-439127	B1	19950511		

AB Compns. and methods of manuf. for producing a medicament compn. capable of absorption through the mucosal tissues of the mouth, pharynx, and esophagus are disclosed. The present invention relates to such compns. and methods which are useful in administering lipophilic and nonlipophilic drugs in a dose-to-effect manner that sufficient drug is administered to produce precisely a desired effect. The invention also relates to a manufg. technique that enables a therapeutic agent or drug to be incorporated into a flavored dissolvable matrix. An appliance or holder is preferably attached to the dissolvable matrix. Employing the present invention the drug may be introduced into the patient's bloodstream almost as fast as through injection, and much faster than using the oral administration route, while avoiding the neg. aspects of both of these methods. The present invention achieves these advantages by incorporating the drug into a carbohydrate, fat, protein, wax, or other dissolvable matrix compn. The dissolvable matrix may include permeation enhancers to increase the drug absorption by the mucosal tissues of the mouth. The matrix compn. may also include pH buffering agents to modify the salival pH thereby increasing the absorption of the drug through the mucosal tissue. Methohexital sodium was incorporated into a dissolvable matrix including citric acid; ribotide; Compritol 888; aspartame; vanilla, wild cherry, and peppermint microcapsules; compressible sugar; and maltodextrin.

L6 ANSWER 69 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 118:116537 CA
TI Increased hypothalamic [3H]flunitrazepam binding in hypothalamic-pituitary-adrenal axis hyporesponsive Lewis rats
AU Smith, Craig C.; Hauser, Elizabeth; Renaud, Nicole K.; Leff, Amy; Aksentijevich, Sofia; Chrousos, George P.; Wilder, Ronald L.; Gold, Philip

W.; Sternberg, Esther M.
CS Unit Neuronendocr. Immunol. Behav., NICHD, Bethesda, MD, 20892, USA
SO Brain Research (1992), 569(2), 295-9
CODEN: BRREAP; ISSN: 0006-8993
DT Journal
LA English
AB The authors previously demonstrated that susceptibility of Lewis (LEW/N) rats to **inflammatory** disease, compared to relatively resistant Fischer (F344/N) rats, is related to deficient glucocorticoid counter-regulation of the immune response resulting from deficient ACTH-releasing hormone (CRH) responsiveness to **inflammatory** and other stress mediators. The **GABA**/benzodiazepine receptor complex is an important neg. modulator of CRH secretion and responsiveness to excitatory stimuli. In this study, the authors have examd. in vitro binding of [3H]flunitrazepam to hypothalamic membrane prepns. from LEW/N and F344/N rats. LEW/N rats had significantly more hypothalamic benzodiazepine binding sites (.beta.max) than F344/N rats, but there were no differences in benzodiazepine binding affinities (Kd) between these two strains. The differences in benzodiazepine receptor no. were consistent with the resp. plasma corticosterone levels in the two strains, and with previous work indicating a neg. correlation between corticosterone levels and benzodiazepine binding site no. Adrenalectomy of F344/N rats increased benzodiazepine binding to levels comparable to LEW/N animals and **treatment** of adrenalectomized F344/N rats with DEX resulted in lowering of benzodiazepine .beta.max to levels that did not differ significantly from those of intact F344/n rats. There was no significant change in receptor no. in either adrenalectomized or DEX-**treated** LEW/N rats. These findings suggest that basal benzodiazepine receptor differences between these strains may be partially related to strain differences in corticosterone levels, however that addnl. factors may contribute to maintenance of these differences in LEW/N rats. Since benzodiazepine attenuate hypothalamic CRH secretion through GABAergic inhibition, the authors suggest that strain differences in receptor no. could also augment strain differences in hypothalamic-pituitary-adrenal axis function through differential sensitivity to **GABA**-mediated feedback.

L6 ANSWER 70 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 116:99210 CA
TI Effects of the combination of new quinolones and a nonsteroidal anti-**inflammatory** drug, fenbufen, on the EEG of rabbits
AU Suzuki, Toshio; Hara, Yukio; Tamagawa, Masaji; Kakizaki, Kazushi; Murayama, Satoshi
CS Sch. Med., Chiba Univ., Chiba, 280, Japan
SO Nippon Yakurigaku Zasshi (1992), 99(1), 45-54
CODEN: NYKZAU; ISSN: 0015-5691
DT Journal
LA Japanese
AB The convulsive effects of combination of fenbufen, a nonsteroidal anti-**inflammatory** drug, and new quinolones, enoxacin, norfloxacin, ofloxacin, ciprofloxacin, lomefloxacin, and tosufloxacin, were tested on the EEG recorded from the neocortex and subcortical regions of the rabbits. Animals **treated** with fenbufen (50-200 mg/kg, p.o.) tended to have a high amplitude slow wave in their EEG. Rabbits **treated** with the new quinolones at the dose of 100 mg/kg, p.o., with the exception of tosufloxacin, also, tended to show a high amplitude slow wave in their EEG. Each new quinolone given 30 min after fenbufen (50 mg/kg, p.o.) elicited characteristic spikes on the EEG. Then, high-frequency-spikes and epileptiform seizure waves appeared for a long exptl. period with this combination. The combination of fenbufen and tosufloxacin (100-400 mg/kg, p.o.) caused no changes in EEG and behavior. The spike and epileptiform wave could be suppressed only temporarily with diazepam (1-4 mg/kg, i.v.). These results suggest that combined use of fenbufen and one of the new quinolones, except for tosuloxacin, produces the seizure. Not only **GABA** but also several other mechanisms in the central nervous system may be involved in the convulsion.

L6 ANSWER 71 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 116:58771 CA

TI Preparation of **GABA** derivatives as anticonvulsants and anti-**inflammatories**
IN Sada, Takuo; Wada, Hiroaki
PA Nisshin Oil Mills, Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 03193758	A2	19910823	JP 1989-335771	19891225
PRAI JP 1989-335771		19891225		

OS MARPAT 116:58771
AB R1COS(CH2)2CH(SCOR2)(CH2)4CONHCH2CHR3CH2CO2H (R1, R2 = H, lower alkyl; R3 = H, OH) (I) or their salts, useful as anti-**inflammatories** (no data) and anticonvulsants, are prepd. **Treatment** of 5.2 g AcS(CH2)2CH(SAc)(CH2)4CO2H (prepn. given) with N-hydroxysuccinimide and DCC in AcOEt at room temp. for 24 h gave 4.2 g the corresponding active ester, which (900 mg) was **treated** with 250 mg **GABA** and NaHCO3 in THF-H2O at room temp. for 48 h to afford 20% I (R1= R2 = Me, R3 = H) (II). II at 250 mg/kg i.p. inhibited the onset of pentylenetetrazole-induced convulsion more strongly than **GABA** in mice.

L6 ANSWER 72 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 115:150811 CA
TI **Treatment** of mammalian spinal cord injury with antioxidants
AU Naftchi, N. Eric
CS Inst. Rehabil. Med., New York Univ. Med. Cent., New York, NY, 10016, USA
SO International Journal of Developmental Neuroscience (1991), 9(2), 113-26
CODEN: IJDND6; ISSN: 0736-5748
DT Journal
LA English
AB After spinal cord injury, cats were **treated** with a combination of methylprednisolone sodium succinate (MP 35 mg/kg) and .epsilon.-aminocaproic acid (EACA 350 mg/kg) or with guanabenz acetate (0.65 mg/kg). Guanabenz acetate was administered twice daily for 8 wk. In the first group, the **treatment** increased blood flow in the abdominal aorta. All cats **treated** with guanabenz acetate 3 h after spinal cord contusion had return of micturition and none suffered complete paraplegia. Four of 8 animals had partial and the other 4 had a complete motor recovery. A superoxide generating system with horseradish peroxidase decreased [14C]**GABA** uptake by mouse cortical slices by 33%. When superoxide dismutase was added to the medium, the uptake was reduced by only 9%. The nerve endings were also protected by superoxide dismutase from morphol. damage by superoxide as obsd. by electron microscopy. The agents used produce their ameliorating effects by their anti-**inflammatory**, antioxidant, and membrane-stabilizing properties, and by enhancing the regional microcirculation. In addn., guanabenz acetate may act also as an .alpha.2-adrenoceptor agonist.

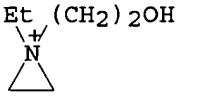
L6 ANSWER 73 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 112:173068 CA
TI Preparation and characterization of novel neuronotropic factor from the brain and its use in **treating** neuropathological conditions
IN Della Valle, Francesco
PA Fidia S.p.A., Italy
SO Eur. Pat. Appl., 27 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 327769	A2	19890816	EP 1988-400365	19880217
EP 327769	A3	19891018		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
US 5218094	A	19930608	US 1990-562024	19900802

PRAI IT 1988-47612 19880208
IT 1986-48370 19860807
IT 1986-48782 19861223
US 1987-79891 19870731
US 1988-153437 19880208

AB A novel neuronotropic factor having a mol. wt. of .apprx. 14,000-17,000 daltons and an isoelec. point of .apprx. 10 is prepd. by homogenization of mammalian brain tissue, particularly bovine brain tissue, acid pptn. of the homogenate thus produced, dialysis of the resulting supernatant with dialysis membranes having a mol. wt. cut-off of between 5 and 10 kilodaltons and chromatog. fractionation by mol. wt. permeation of the dialyzed supernatant thus produced. The neuronotropically active fractions may be further purified by cation exchange chromatog. with a gradient of ammonium acetate buffer. The neuronotropic factor of the invention is useful in the **treatment** of various neuropathol. conditions, e.g. traumatic injury, Alzheimer's disease, Parkinson's disease, and multiple sclerosis. An injection compn. was prepd. contg. the neuronotropic factor 5 .mu.g, NaCl 16 mg, and pH 7 citrate buffer 2 mL.

L6 ANSWER 74 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 108:144908 CA
TI Biochemical and histological modifications of the rat retina induced by the cholinergic neurotoxin AF64A
AU Estrada, Carmen; Triguero, Domingo; Martin del Rio, Rafael; Gomez Ramos, Pilar
CS Fac. Med., Univ. Auton. Madrid, Madrid, 28029, Spain
SO Brain Research (1988), 439(1-2), 107-15
CODEN: BRREAP; ISSN: 0006-8993
DT Journal
LA English
GI



I

AB Intraocular injections of ethylcholine mustard aziridinium ion (AF 64A) (I) in the rat depressed retinal choline acetyltransferase (ChAT) activity in a dose-dependent manner without any change in the content of amino acid neurotransmitters **GABA**, glycine, aspartate, and glutamate. ChAT redn. was already detected 24 h after the injection and persisted for at least 1 mo. In vitro AF 64A also inhibited retinal ChAT activity. No changes in muscarinic receptor sites were detected. The histol. study showed light cells, characterized by cytoplasmic swelling in the innermost part of the inner nuclear layer and in the ganglion cell layer. Apparently, these light cells are the cholinergic retinal neurons affected by the toxin. Dark cells in the inner nuclear layer, large empty spaces in the outer nuclear layer, **inflammatory** infiltrate, and vascular alterations were also obsd. in **treated** retinas. Choline uptake systems in photoreceptors and in endothelial cells or cholinergic perivascular nerve endings may explain the lesions obsd. in the outer nuclear layer and the vascular alterations.

L6 ANSWER 75 OF 75 CA COPYRIGHT 2003 ACS on STN
AN 107:141130 CA
TI Analgesic composition and method of relieving pain
IN Rosenberg, Barnett
PA USA
SO U.S., 9 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

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PI   US 4665069        A    19870512       US 1985-719239   19850402
PRAI US 1985-719239         19850402
AB   An analgesia compn. comprises an aq. soln. of a parasympathomimetic agent
     in a concn. of .apprx.10-3-10-13 g/mL and a method of relieving pain
     comprises topically applying the compn. to the genitalia of a human or an
     animal.  Knee joint pain and muscle cramps in humans not responding to
     chiropractic treatments or aspirin, resp., were eliminated
     completely by application to the genitals of a nicotine bitartrate soln.
     (0.1 mL; 10-9 g/mL) .gtoreq.1 time/wk.


=> file medline
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                     182.70     182.91

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)            SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                     -46.50     -46.50

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 MeSH 2003 vocabulary.  See http://www.nlm.nih.gov/mesh/changes2003.html
 for a description on changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> search l6
         34295 GABA
        261050 INFLAM?
       1909474 TREAT?
L7           66 L4 AND L5

=> dis l7 1- bib abs
YOU HAVE REQUESTED DATA FROM 66 ANSWERS - CONTINUE? Y/(N):y

L7   ANSWER 1 OF 66     MEDLINE on STN
AN   2003378207     MEDLINE
DN   22764852   PubMed ID: 12883408
TI   Thiopental inhibits tumor necrosis factor alpha-induced activation of
     nuclear factor kappaB through suppression of kappaB kinase activity.
AU   Loop Torsten; Humar Matjaz; Pischke Soeren; Hoetzel Alexander; Schmidt
     Rene; Pahl Heike L; Geiger Klaus K; Pannen Benedikt H J
CS   Department of Anesthesiology and Critical Care Medicine, University
     Hospital, Freiburg, Germany.
SO   ANESTHESIOLOGY, (2003 Aug) 99 (2) 360-7.
     Journal code: 1300217. ISSN: 0003-3022.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Abridged Index Medicus Journals; Priority Journals
EM   200308
ED   Entered STN: 20030814
     Last Updated on STN: 20030829
     Entered Medline: 20030828
AB   BACKGROUND: Thiopental is frequently used for the treatment of
     intracranial hypertension after severe head injury and is associated with
     immunosuppressive effects.  The authors have recently reported that
     thiopental inhibits activation of nuclear factor (NF) kappaB, a
     transcription factor implicated in the expression of many
     inflammatory genes.  Thus, it was the aim of the current study to
     examine the molecular mechanism of this inhibitory effect.  METHODS: The
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authors tested gamma-aminobutyric acid (**GABA**), the **GABA** (A) antagonist bicuculline, and the **GABA**(B) antagonist dichlorophenyl-methyl-amino-propyl-diethoxymethyl-phosphinic acid (CGP 52432) in combination with thiopental for their influence on the activation of NF-kappaB. In addition, they investigated the direct effect of thiopental on activated NF-kappaB DNA binding activity. These experiments were conducted in Jurkat T lymphocytes using electrophoretic mobility shift assays. The presence of the phosphorylated and dephosphorylated NF-kappaB inhibitor IkappaBalpha (Western blotting) and IkappaB kinase activity were studied in Jurkat T cells and human CD3+ T lymphocytes. In addition, the authors tested the effect of the structural barbiturate analog pairs thiopental-pentobarbital and thiamylal-secobarbital and of thiopental in combination with the thio-group containing chemical dithiothreitol on the activation of NF-kappaB. RESULTS: **GABA** did not inhibit NF-kappaB activation, and the **GABA**(A) and **GABA**(B) antagonists bicuculline and CGP did not diminish the thiopental-mediated inhibitory effect on NF-kappaB activation. Thiopental did not inhibit activated NF-kappaB directly in a cell-free system. The phosphorylation of IkappaBalpha was prevented after incubation with 1,000 microg/ml thiopental. The same concentration of thiopental also inhibited IkappaB kinase activity in tumor necrosis factor-stimulated Jurkat T cells and human CD3+ T lymphocytes (60% suppression, $P < 0.05$ vs. tumor necrosis factor alpha alone). Thiobarbiturates (4 x 10(-3) m) inhibited NF-kappaB activity, whereas equimolar concentrations of the structural oxyanalogs did not. Preincubation of thiopental with dithiothreitol diminished the inhibitory effect. CONCLUSION: Thiopental-mediated inhibition of NF-kappaB activation is due to the suppression of IkappaB kinase activity and depends at least in part on the thio-group of the barbiturate molecule.

L7 ANSWER 2 OF 66 MEDLINE on STN
AN 2003134864 MEDLINE
DN 22536127 PubMed ID: 12649368
TI Differential regulation of **GABA** B receptor subunit expression and function.
AU Sands S A; McCarson K E; Enna S J
CS Department of Pharmacology, Toxicology and Therapeutics, Kansas University School of Medicine, Kansas City, Kansas 66160-7424, USA.
NC DA 12505 (NIDA)
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (2003 Apr) 305 (1) 191-6.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200304
ED Entered STN: 20030322
Last Updated on STN: 20030423
Entered Medline: 20030422
AB The **GABA**(B) receptor is a G protein-coupled heterodimer composed of **GABA**(B1) and **GABA**(B2) subunits. In the present study, experiments were undertaken to examine the relationship between **GABA**(B) receptor function and subunit expression in the rat lumbar spinal cord following pharmacological and physiological manipulation of this receptor system. Although formalin-induced hind paw **inflammation** increases the production of **GABA**(B1) and **GABA**(B2) protein in the spinal cord within 24 h, there is no change in receptor function, as measured by the baclofen-stimulated guanosine 5'-O-(3-[(35)S]thiotriphosphate) ([(35)S]GTPgammaS) binding assay. Conversely, although chronic (7 days) administration of baclofen, a **GABA**(B) receptor agonist, abolishes baclofen-stimulated [(35)S]GTPgammaS binding in the spinal cord tissue, causes tolerance to the sedative and antinociceptive effects of the drug, increases the number of formalin-induced hind paw flinches, and induces mechanical hyperalgesia, this **treatment** had no effect on the levels of **GABA**(B1) or **GABA**(B2) mRNAs in the lumbar spinal cord. The results indicate a lack of concordance between expression of **GABA**(B1) and **GABA**(B2) subunits and **GABA**(B)

receptor function, suggesting these subunit proteins may serve multiple functions in the cells. Moreover, these findings indicate that nongenomic mechanisms are primarily responsible for the **GABA**(B) receptor desensitization that occurs during prolonged exposure to receptor agonist.

L7 ANSWER 3 OF 66 MEDLINE on STN
AN 2003001459 MEDLINE
DN 22395889 PubMed ID: 12507405
TI Neuroprotective agents for the **treatment** of acute ischemic stroke.
AU Ovbiagele Bruce; Kidwell Chelsea S; Starkman Sidney; Saver Jeffrey L
CS Stroke Center and Department of Neurology, University of California at Los Angeles, 710 Westwood Plaza, Los Angeles, CA 90095, USA.. Ovibes@mednet.ucla.edu
SO Curr Neurol Neurosci Rep, (2003 Jan) 3 (1) 9-20. Ref: 78
Journal code: 100931790. ISSN: 1528-4042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200305
ED Entered STN: 20030102
Last Updated on STN: 20030515
Entered Medline: 20030514
AB Neuroprotective **treatments** are therapies designed to interrupt the cellular, biochemical, and metabolic elaboration of injury during or following exposure to ischemia; they encompass a rapidly expanding array of pharmacologic interventions. Various classes of neuroprotective agents have reached phase III efficacy trials in focal ischemic stroke, but none has proven effective, despite successful preceding animal studies. This notwithstanding, recent favorable results of hypothermia in human cardiac arrest trials have validated the general concept of neuroprotection. In addition, the promise of neuroprotective therapy for focal acute ischemic stroke has been renewed by innovations in strategies of preclinical drug development and clinical trial design that rectify past defects, including trial testing of combination therapies rather than single agents and novel approaches to accelerating time to initiation of experimental **treatment**.

L7 ANSWER 4 OF 66 MEDLINE on STN
AN 2002736344 MEDLINE
DN 22336836 PubMed ID: 12446004
TI IL-4 increases GABAergic phenotype in rat retinal cell cultures: involvement of muscarinic receptors and protein kinase C.
AU Sholl-Franco Alfred; Marques Patricia M B; Ferreira Cecilia M C; de Araujo Elizabeth G
CS Departamento de Neurobiologia, Programa de Neuroimunologia, Instituto de Biologia, Centro de Estudos Gerais, Universidade Federal Fluminense, CP# 100180, RJ 24001-970, RJ, Niteroi, Brazil.
SO JOURNAL OF NEUROIMMUNOLOGY, (2002 Dec) 133 (1-2) 20-9.
Journal code: 8109498. ISSN: 0165-5728.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200301
ED Entered STN: 20021227
Last Updated on STN: 20030115
Entered Medline: 20030114
AB Interleukin-4 (IL-4) is an anti-**inflammatory** cytokine. During injuries, infections and neurodegenerative diseases, high levels of this molecule are expressed in the brain. In the present work, we investigated the effect of IL-4 on GABAergic differentiation of retinal cells kept in vitro. We analyzed either the uptake of [3H]-gamma-aminobutyric acid (**GABA**) or the expression of glutamic acid decarboxylase (GAD-67) following IL-4 **treatment**. We have also investigated the pharmacological modulation of the [3H]-**GABA** uptake by

cholinergic activation. Our results demonstrate that IL-4 increases the uptake of [3H]-**GABA** after 48 h in culture in a dose-dependent manner (0.5-100 U/ml). The maximal effect was obtained with 5 U/ml (75% increase). This effect was blocked by 1 mM of nipecotic acid, demonstrating the involvement of the GAT-1 subtype of **GABA** transporter. The IL-4 effect depends on M1 muscarinic activity, an increase in intracellular calcium levels, tyrosine kinase activity and protein kinase C (PKC) activity. **Treatment** with IL-4 for 48 h induced an increase of 90% in the number of GAD- and **GABA** -immunoreactive cells when compared with control cultures. Our results indicate that IL-4 modulates the GABAergic phenotype of retinal cells in culture. This result can suggest an important role for this cytokine either during the normal development of retinal circuitry or during neuroprotection after injuries.

L7 ANSWER 5 OF 66 MEDLINE on STN
AN 2002726476 MEDLINE
DN 22377063 PubMed ID: 12487727
TI Differential induction of midazolam metabolism in the small intestine and liver by oral and intravenous dexamethasone pretreatment in rat.
AU Eeckhoudt S L; Horsmans Y; Verbeeck R K
CS Department of Pharmaceutical Sciences, Catholic University of Louvain, B-1200 Brussels, Belgium.
SO XENOBIOTICA, (2002 Nov) 32 (11) 975-84.
Journal code: 1306665. ISSN: 0049-8254.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200306
ED Entered STN: 20021219
Last Updated on STN: 20030617
Entered Medline: 20030616
AB 1. Midazolam is metabolized in the rat by CYP3A enzymes to 4-OH-midazolam (4-OH-MDZ) and 1'-OH-midazolam (1'-OH-MDZ). The induction of midazolam metabolism was studied in male Wistar rats **treated** with dexamethasone (50 mg kg(-1) day(-1)) during 4 days via the oral or intravenous routes. Microsomes were prepared from the liver and the proximal small intestine and in vitro metabolism of midazolam was determined. In addition, CYP3A1- and CYP3A2-like protein levels were measured by gel electrophoresis and immunoblotting. 2. The V(max)'s (mean SEM) for 4-OH-MDZ and 1'-OH-MDZ formation were much lower in intestinal (0.078 +/- 0.002 and 0.074 +/- 0.002 microM min(-1) mg(-1) protein, respectively) compared with hepatic microsomes prepared from the uninduced rat (0.870 +/- 0.007 and 0.310 +/- 0.020 microM min(-1) mg(-1) protein, respectively). Induction by oral or intravenous dexamethasone pretreatment led to significant increases in V(max) for 4-OH-MDZ and 1'-OH-MDZ by both intestinal and hepatic microsomes. Oral dexamethasone pretreatment via the oral route resulted in a more pronounced increase in V(max) compared with intravenous administration of the inducer. 3. CYP3A1 and CYP3A2 protein levels in liver microsomes were significantly increased following oral (3.7- and 3.2-fold, respectively) or intravenous (2.6- and 2.1-fold, respectively) pretreatment with dexamethasone. On the contrary, only oral dexamethasone pretreatment resulted in a significant change in intestinal CYP3A2-like protein (7.3-fold). A slight difference in the migration distance of the immunoreactive band for CYP3A2 was also observed for intestinal microsomes. 4. These results suggest that intestinal CYP3A enzymes in the rat differ from hepatic CYP3A1 and CYP3A2. They also demonstrate that systemic dexamethasone administration can induce intestinal microsome activity.

L7 ANSWER 6 OF 66 MEDLINE on STN
AN 2002673857 MEDLINE
DN 22299393 PubMed ID: 12411814
TI Gabapentin and pregabalin can interact synergistically with naproxen to produce antihyperalgesia.
AU Hurley Robert W; Chatterjea Debika; Rose Feng Meihua; Taylor Charles P; Hammond Donna L
CS Department of Anesthesia and Critical Care, and Committee on Neurobiology,

University of Chicago, Illinois, USA.
SO ANESTHESIOLOGY, (2002 Nov) 97 (5) 1263-73.
Journal code: 1300217. ISSN: 0003-3022.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200211
ED Entered STN: 20021119
Last Updated on STN: 20021214
Entered Medline: 20021127
AB BACKGROUND: Gabapentin and pregabalin are anticonvulsants with antihyperalgesic effects in animal models of neuropathic and **inflammatory** nociception. This study characterized the manner in which gabapentin or pregabalin interacts with naproxen to suppress thermal hyperalgesia and **inflammation** in the carrageenan model of peripheral **inflammation**. METHODS: Gabapentin, pregabalin, naproxen, or a fixed-dose ratio of gabapentin + naproxen or pregabalin + naproxen was administered orally to rats after the induction of **inflammation** by intraplantar injection of lambda-carrageenan in one hind paw. Nociceptive thresholds were determined by the radiant heat paw-withdrawal test. Paw edema was measured by plethysmometry. Drug plasma concentrations were determined by a liquid chromatography-mass spectroscopy-mass spectroscopy method. RESULTS: Gabapentin, pregabalin, and naproxen alone reversed thermal hyperalgesia with ED50 values of 19.2, 6.0, and 0.5 mg/kg, respectively. Mixtures of gabapentin + naproxen in fixed-dose ratios of 50:1, 10:1, or 1:1 interacted synergistically to reverse carrageenan-induced thermal hyperalgesia. However, 1:50 gabapentin + naproxen produced only additive effects. No combination of gabapentin + naproxen decreased paw edema in a manner greater than additive. Plasma concentrations of gabapentin and naproxen were unaltered by the addition of the other drug. The mixture of 10:1 of pregabalin + naproxen interacted synergistically to reverse thermal hyperalgesia on the **inflamed** hind paw, whereas mixtures of 1:1 or 1:10 produced additive effects. CONCLUSIONS: These data suggest that gabapentin + naproxen and pregabalin + naproxen can interact synergistically or additively to reverse thermal hyperalgesia associated with peripheral **inflammation**. Therefore, the use of gabapentin or pregabalin in low-dose combinations with naproxen may afford therapeutic advantages for clinical **treatment** of persistent **inflammatory** pain.

L7 ANSWER 7 OF 66 MEDLINE on STN
AN 2002661624 MEDLINE
DN 22308821 PubMed ID: 12421115
TI Non-cholinergic strategies for **treating** and preventing Alzheimer's disease.
AU Doraiswamy P Murali
CS Department of Psychiatry, Duke University Medical Center, Durham, North Carolina 27710, USA.
SO CNS Drugs, (2002) 16 (12) 811-24. Ref: 115
Journal code: 9431220. ISSN: 1172-7047.
CY New Zealand
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200304
ED Entered STN: 20021108
Last Updated on STN: 20030406
Entered Medline: 20030404
AB The pathophysiology of Alzheimer's disease is complex and involves several different biochemical pathways. These include defective beta-amyloid (Abeta) protein metabolism, abnormalities of glutamatergic, adrenergic, serotonergic and dopaminergic neurotransmission, and the potential involvement of **inflammatory**, oxidative and hormonal pathways. Consequently, these pathways are all potential targets for Alzheimer's disease **treatment** and prevention strategies. Currently, the mainstay **treatments** for Alzheimer's disease are the

cholinesterase inhibitors, which increase the availability of acetylcholine at cholinergic synapses. Since the cholinesterase inhibitors confer only modest benefits, additional non-cholinergic Alzheimer's disease therapies are urgently needed. Several non-cholinergic agents are currently under development for the **treatment** and/or prevention of Alzheimer's disease. These include anti-amyloid strategies (e.g. immunisation, aggregation inhibitors, secretase inhibitors), transition metal chelators (e.g. clioquinol), growth factors, hormones (e.g. estradiol), herbs (e.g. Ginkgo biloba), nonsteroidal anti-**inflammatory** drugs (NSAIDs, e.g. indomethacin), antioxidants, lipid-lowering agents, antihypertensives, selective phosphodiesterase inhibitors, vitamins (E, B12, B6, folic acid) and agents that target neurotransmitter or neuropeptide alterations. Neurotransmitter receptor-based approaches include agents that modulate certain receptors (e.g. nicotinic, muscarinic, alpha-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid [AMPA], gamma-aminobutyric acid [**GABA**], N-methyl-D-aspartate [NMDA]) and agents that increase the availability of neurotransmitters (e.g. noradrenergic reuptake inhibitors). Of these strategies, the NMDA receptor antagonist memantine is in the most advanced stage of development in the US and is already approved in Europe as the first **treatment** for moderately severe to severe Alzheimer's disease. Memantine is proposed to counteract cellular damage due to pathological activation of NMDA receptors by glutamate. Results with Ginkgo biloba have been mixed. Data for neurotrophic therapies and vitamin E (tocopherol) appear promising but require confirmation. NSAIDs and conjugated estrogens have not proven to be of value to date for the **treatment** of Alzheimer's disease. Statins may have a potential role in reducing the risk or delaying the onset of Alzheimer's disease, although this has yet to be confirmed in randomised trials. There are currently no data to support the use of statins as a **treatment** for dementia. This article provides an update on the current status of selected agents, focusing primarily on those agents with the most extensive clinical evidence at present.

L7 ANSWER 8 OF 66 MEDLINE on STN
AN 2002488590 MEDLINE
DN 22235952 PubMed ID: 12323392
TI Involvement of the peripheral benzodiazepine receptor in the development of rheumatoid arthritis in Mrl/lpr mice.
AU Bribes Estelle; Bourrie Bernard; Esclangon Martine; Galiegue Sylvaine; Vidal Hubert; Casellas Pierre
CS Departement Immunologie-Oncologie, Sanofi-Synthelabo Recherche, 371, avenue du Professeur Blayac, 34184 Montpellier Cedex 04, France.. estelle.bribes@sanofi-synthelabo.com
SO EUROPEAN JOURNAL OF PHARMACOLOGY, (2002 Sep 27) 452 (1) 111-22. Journal code: 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200303
ED Entered STN: 20020927
Last Updated on STN: 20030319
Entered Medline: 20030318
AB In this study, the effects of different peripheral benzodiazapine receptor ligands: PK 11195 [1-(2-chloro-phenyl)-N-methyl-N-(1-methylpropyl)-1-isoquinoline carboxamide], Ro5-4864 [7-chloro-5-(4-chlorophenyl)-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one] and the newly described SSR 180575 (7-chloro-N,N,5-trimethyl-4-oxo-3-phenyl-3,5-dihydro-4H-pyridozine[4,5-b] indole-1-acetamide) were analysed on the progression and severity of rheumatoid arthritis in vivo in the Mrl/lpr mice model, following chronic **treatment** (at 3 mg/kg, i.p. for 30 days). We found that peripheral benzodiazepine receptor ligands have significant beneficial therapeutic action on the development of spontaneous rheumatoid arthritis-like signs. Concomitantly, we mapped immunoreactive peripheral benzodiazepine receptor in **inflamed** tissues, and we observed that in addition to the infiltrated leukocytes, peripheral benzodiazepine receptor was expressed in synovial membranes, at the cartilage pannus junction and in chondrocytes. Interestingly, we observed that peripheral

benzodiazepine receptor expression in chondrocytes was reduced when Mrl/lpr mice developed the pathology and restored upon peripheral benzodiazepine receptor ligand **treatment**. Altogether, our data provide further evidence of a role played by peripheral benzodiazepine receptor in the regulation of **inflammation** processes and support new therapeutic applications for specific potent peripheral benzodiazepine receptor ligands.

L7 ANSWER 9 OF 66 MEDLINE on STN
AN 2002482379 MEDLINE
DN 22229706 PubMed ID: 12244293
TI [Clinical use of spinal or epidural steroids].
Uso degli steroidi per via spinale ed epidurale.
AU Marinangeli F; Ciccozzi A; Donatelli F; Paladini A; Varrassi G
CS Dipartimento di Discipline Chirurgiche, Cattedra di Anestesia e Rianimazione, Universita degli Studi, L'Aquila, Italy.
SO MINERVA ANESTESIOLOGICA, (2002 Jul-Aug) 68 (7-8) 613-20. Ref: 79
Journal code: 0375272. ISSN: 0375-9393.
CY Italy
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA Italian
FS Priority Journals
EM 200211
ED Entered STN: 20020924
Last Updated on STN: 20021214
Entered Medline: 20021126
AB Steroids, drugs with potent antiinflammatory properties on the damaged nervous roots, have been especially used as adjuvants of local anesthetics, by spinal route, in the **treatments** of low-back pain. Spinal route was chosen to obtain a higher local concentration of drug, with few systemic side effects and to improve drug's action mechanism. Steroids seem to interact with **GABA** receptors and thus control neural excitability through a stabilising effect on membranes, modification of nervous conduction and membrane hyperpolarization, in supraspinal and spinal site. Epidural steroids are especially used in the **treatment** of low back pain due to irritation of nervous roots. They have been administered alone or in association with local anesthetics and/or saline solution. Slow release formulations have been generally used (methylprednisolone acetate, and triamcinolone diacetate). Other indications of epidural steroids are: postoperative hemilaminectomy pain, prevention of post herpetic neuralgia, degenerative ostheoartrithis. Intra-thecal steroids have been frequently used in the **treatment** of lumbar radiculopathy due to discopathy, as an alternative **treatment** when epidural administration is ineffective. Positive results have been obtained with methylprednisolone acetate, alone or in association with local anesthetics. Complications related to intraspinal steroids injections are due to execution of the block and side effects of drugs. Complications associated with intrathecal steroids are more frequent and severe than epidural injections and include: adhesive arachnoiditis, aseptic meningitis, cauda equina syndrome. Steroidal toxicity seems to be related to the polyethylenic glycole vehicle. Anyway, slow release formulations contain less concentrated polyethylenic glycole. The epidural administration, a correct dilution of steroid with local anesthetics solution and/or saline solution, and a limited number of injections (no more than three) allows a significant reduction of steroid neurotoxicity.

L7 ANSWER 10 OF 66 MEDLINE on STN
AN 2002426680 MEDLINE
DN 22171046 PubMed ID: 12183658
TI Pregabalin (CI-1008) inhibits the trinitrobenzene sulfonic acid-induced chronic colonic allodynia in the rat.
AU Diop Laurent; Raymond Frederic; Fargeau Helene; Petoux Francine; Chovet Maria; Doherty Annette M
CS Department of Pharmacology, Pfizer Global Research, Fresnes Laboratories 3-9, rue de la Loge, BP-100 Fresnes Cedex, France..

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SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (2002 Sep) 302 (3) 1013-22.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200209
ED Entered STN: 20020817
Last Updated on STN: 20020919
Entered Medline: 20020918
AB In human, digestive disorders are often associated with visceral pain. In these pathologies, visceral pain threshold is decreased indicating a visceral hypersensitivity. Pregabalin [CI-1008; S-(+)-3-isobutylgaba] presents antihyperalgesic actions in **inflammatory** somatic pain models. This study was designed to evaluate 1) the effect of injection of TNBS into the colon on visceral pain threshold, and 2) the antihyperalgesic effect of pregabalin on TNBS-induced chronic colonic allodynia. A significant decrease in the colonic pain threshold was observed in trinitrobenzene sulfonic acid (TNBS)-**treated** animals (17.8 +/- 1.27 versus 43.4 +/- 1.98 mm Hg). Pregabalin (30-200 mg/kg s.c.) and morphine (0.1-1 mg/kg s.c.) showed a dose-related inhibition of TNBS-induced colonic allodynia. Pregabalin did not inhibit the colonic **inflammatory** effect of TNBS. In normal conditions (control animals), morphine (0.3 mg/kg s.c.) significantly increased the colonic pain threshold, whereas pregabalin (200 mg/kg s.c.) did not modify the colonic pain threshold. Pregabalin suppressed the TNBS-induced colonic allodynia but did not modify the colonic threshold in normal conditions. The ability of pregabalin to block the chronic colonic allodynia indicates that it is effective in abnormal colonic hypersensitivity, suggesting a possible effect in chronic pain in irritable bowel syndrome.

L7 ANSWER 11 OF 66 MEDLINE on STN
AN 2002382821 MEDLINE
DN 22126832 PubMed ID: 12127027
TI Increased synaptosomal [3H] **GABA** uptake in the rat brainstem after facial carrageenan injections.
AU Ng Chee-Hon; Ong Wei-Yi
CS Department of Anatomy, National University of Singapore, Singapore 119260.
SO PAIN, (2002 Aug) 98 (3) 259-68.
Journal code: 7508686. ISSN: 0304-3959.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200210
ED Entered STN: 20020720
Last Updated on STN: 20021024
Entered Medline: 20021023
AB The aim of the present study was to quantify synaptosomal [(3)H] gamma aminobutyric acid (**GABA**) uptake in the rat brainstem after facial carrageenan injections. Synaptosomal preparations from the brainstem of rats that had received one or four facial carrageenan injections showed greater **GABA** binding on the side of the brainstem ipsilateral to the carrageenan injection than on the contralateral side when compared to saline injected controls. In contrast, no difference in **GABA** binding between the injected and contralateral sides was observed in the same synaptosomal preparations that had been **treated** with **GABA** uptake inhibitors NNC-711, beta-alanine, or nipecotic acid. The difference between **GABA** binding in the absence of the **GABA** uptake inhibitor and **GABA** binding in a portion from the same synaptosomal preparation which had been incubated with the **GABA** uptake inhibitor was obtained to represent [(3)H] **GABA** binding to **GABA** transporters/transporter mediated [(3)H] **GABA** uptake. A significantly greater **GABA** uptake was observed on the side of the brainstem ipsilateral to the carrageenan injection(s) than on the contralateral side. A consequence of the observed increase in

GABA uptake is that it could reduce the amount of **GABA** in the synaptic cleft. This could influence the transmission of nociceptive input from primary afferents to secondary neurons in the spinal trigeminal nucleus and could be a contributing factor in the development of hyperalgesia after carrageenan injections or other chronic **inflammatory** conditions.

L7 ANSWER 12 OF 66 MEDLINE on STN
AN 2002264907 MEDLINE
DN 21999870 PubMed ID: 12005107
TI Counteraction of the rapid tolerance to 8-hydroxy-2-(di-n-propylamino)tetralin-induced hypothermia in rats by activation of the GABAA receptor-chloride channel complex.
AU Kelder Diana; Ross Svante B
CS Bioscience, Local Discovery, AstraZeneca R & D, Sodertalje, Sweden.
SO PHARMACOLOGY AND TOXICOLOGY, (2002 Jan) 90 (1) 14-9.
Journal code: 8702180. ISSN: 0901-9928.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200208
ED Entered STN: 20020514
Last Updated on STN: 20020823
Entered Medline: 20020822
AB The effects of compounds that open the GABAA receptor-chloride channel complex on the rapidly developed tolerance to the 8-hydroxy-2-(di-n-propylamino)tetralin hydrobromide(8-OH-DPAT)-induced hypothermia in rats were examined. The test compound was injected 15 min. before 1 mg/kg subcutaneous 8-OH-DPAT or saline and 24 hr later a challenge dose of 0.1 mg/kg subcutaneous 8-OH-DPAT was given. The rectal temperature was measured before the challenge dose and 30, 60, 90 and 120 min. thereafter. The hypothermic effect was calculated as the area under the curve. It was found that all the GABAergic compounds examined significantly counteracted the 8-OH-DPAT-induced tolerance to the hypothermic response: muscimol at 3 mg/kg subcutaneous, diazepam at 1 - 3 mg/kg subcutaneous, pentobarbitone sodium at 20 mg/kg subcutaneous, and chlormethiazole at 40 mg/kg subcutaneous. Combined **treatment** of the rats with the GABAA receptor antagonist, bicucculine, or the GABAA receptor-chloride channel blocker, picrotoxin and diazepam, pentoparbitone sodium or chlormethiazole significantly antagonised this counteraction of the 8-OH-DPAT-induced tolerance. Depletion of 5-HT by pretreatment of the rats with the tryptophan hydroxylase inhibitor p-chlorophenylalanine did not counteract the 8-OH-DPAT-induced tolerance to the hypothermic response. Pretreatment of the rats with dexamethazone did not change the development of the tolerance to 8-OH-DPAT-induced hypothermic effect which seems to exclude the involvement of the hypothalamo-pituitary-adrenocortical axis in the tolerance development. It is concluded that the results support the hypothesis that **GABA** neurones beyond the 5-HT neurones are involved in the mechanism causing tolerance to the 5-HT1A receptor-mediated hypothermia in rats.

L7 ANSWER 13 OF 66 MEDLINE on STN
AN 2002262062 MEDLINE
DN 21997505 PubMed ID: 12002834
TI Medical and physical therapy of temporomandibular joint disk displacement without reduction.
CM Comment in: Cranio. 2002 Oct;20(4):238-40; discussion 240-1
AU Stiesch-Scholz Meike; Fink Matthias; Tschernitschek Harald; Rossbach Albrecht
CS Department of Prosthodontics, Medical University of Hannover, Germany.. ms@prothetik.zmk.mh-hannover.de
SO CRANIO, (2002 Apr) 20 (2) 85-90.
Journal code: 8609491. ISSN: 0886-9634.
CY United States
DT (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English

FS Dental Journals
EM 200208
ED Entered STN: 20020511
Last Updated on STN: 20020806
Entered Medline: 20020805
AB The objective of this study was to determine the influence of medical and physical therapy on long-term **treatment** outcome in 72 patients with anterior disk displacement without reduction. Patients were **treated** solely with occlusal splints (group I), with splints and supplementary medical therapy (group II), with splints and physical therapy (group III) or with splints, medical, and physical therapy (group IV). After therapy, the maintenance of improvement was objectively and subjectively assessed with an extensive clinical examination and a postal questionnaire. The percentage of pain free patients after therapy was 76% in group I, 88% in group II, 43% in group III, and 65% in group IV. There was a statistically significant higher increase of maximum jaw opening after therapy in group II than in the control groups ($p<0.05$). The improvement in mouth opening came to 9.7 mm in group I, 14.5 mm in group II, 7.3 mm in group III, and 11.2 mm in group IV. Medical therapy seems to have a positive influence on the **treatment** outcome of patients with anterior disk displacement without reduction.

L7 ANSWER 14 OF 66 MEDLINE on STN
AN 2002228005 MEDLINE
DN 21962307 PubMed ID: 11964518
TI Age-dependent changes in 24-hour rhythms of thymic and circulating growth hormone and adrenocorticotropin in rats injected with Freund's adjuvant.
AU Esquifino A I; Garcia Bonacho M; Arce A; Cutrera R A; Cardinali D P
CS Departamento de Bioquimica y Biologia Molecular III, Facultad de Medicina, Universidad Complutense, Madrid, Spain.
SO NEUROIMMUNOMODULATION, (2001) 9 (5) 237-46.
Journal code: 9422763. ISSN: 1021-7401.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200207
ED Entered STN: 20020420
Last Updated on STN: 20020713
Entered Medline: 20020712
AB OBJECTIVE: To analyze the 24-hour changes in thymic and serum concentration of growth hormone (GH) and adrenocorticotropin (ACTH) and their correlation with thymic concentrations of glutamate, aspartate, taurine and **GABA** in young and old rats during the acute phase of adjuvant's arthritis. METHODS: Young (50-day-old) and old (18-month-old) rats were injected subcutaneously with Freund's adjuvant or its vehicle (paraffin oil containing 15% mannide monooleate). Eighteen days later, they were killed at six different time intervals throughout a 24-hour cycle. Serum and thymic levels of GH and ACTH were measured by radioimmunoassay. Thymic amino acid concentration was measured by HPLC. A quantitative assessment of arthritis was made in an independent group of rats by plethysmography. RESULTS: Old rats injected with Freund's adjuvant exhibited fewer clinical signs of **inflammation** than young rats. Significant 24-hour changes in thymic and serum GH occurred, except for serum GH in adjuvant's vehicle-**treated** old rats. Aging augmented thymic GH and decreased serum GH. Immunization with Freund's adjuvant did not modify GH concentration. Thymic and serum concentration of GH correlated negatively. Thymic ACTH varied significantly over 24 h with maxima during the dark phase, except in Freund's adjuvant-**treated** young rats. Maximal serum ACTH levels occurred in the late afternoon except in Freund's adjuvant-**treated** old rats which showed maxima at night. Immunization with Freund's adjuvant augmented thymic and circulating concentrations of ACTH. Thymic and serum concentration of ACTH correlated positively. Thymic concentration of glutamate, aspartate and taurine decreased in aged rats and correlated significantly with thymic ACTH. CONCLUSION: The results support the existence of a thymic compartment of GH and ACTH that may be independently regulated.

L7 ANSWER 15 OF 66 MEDLINE on STN
AN 2002102265 MEDLINE
DN 21671424 PubMed ID: 11813268
TI Upregulation of mitochondrial peripheral benzodiazepine receptor expression by cytokine-induced damage of human pancreatic islets.
AU Trincavelli M Letizia; Marselli Lorella; Falleni Alessandra; Gremigni Vittorio; Ragge Esther; Dotta Francesco; Santangelo Carmela; Marchetti Piero; Lucacchini Antonio; Martini Claudia
CS Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, Universita di Pisa, Via Bonnanno 6, 56126 Pisa, Italy.
SO JOURNAL OF CELLULAR BIOCHEMISTRY, (2002) 84 (3) 636-44.
Journal code: 8205768. ISSN: 0730-2312.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200203
ED Entered STN: 20020209
Last Updated on STN: 20020320
Entered Medline: 20020319
AB Cytokines produced by immune system cells infiltrating pancreatic islets are candidate mediators of islet beta-cell destruction in autoimmune insulin-dependent diabetes mellitus. After 72 h exposure of human pancreatic islets to a cytotoxic cytokine combination of interleukin 1 beta (50 U/ml), tumor necrosis factor alpha (1,000 U/ml), and interferon gamma (1,000 U/ml), an increase of cell death vs. control islets was demonstrated by TUNEL and cell death detection ELISA method. Islet death was associated with apoptosis and mitochondrial swelling as evidenced by electron microscopy. This effect was correlated with a marked decrease of Bcl-2 mRNA expression (without any major change of Bax mRNA) and a marked increase of inducible nitric oxide synthase mRNA. Since peripheral benzodiazepine receptors constitute the aspecific mitochondrial permeability transition pore, and that it has been suggested to be involved in cytokine-induced cell death, we evaluated the effects of the cytotoxic cytokines on PBR density and mRNA expression. We demonstrated that cytokine **treatment** of human islets induced an increase of maximum density of (3)H1-(2-chlorophenyl-N-methyl-1-methylpropyl)-3-isoquinolinecarboxamide binding sites, (5,110+/-193 vs. 3,421+/-336 fmol/mg proteins, P<0.05) with no significant change in the affinity constant value (9.45+/-0.869 vs. 8.7+/-1.159 nM). Moreover, an increase of the expression of peripheral benzodiazepine receptor mRNA was observed, suggesting an increased transcription from the coding gene. These results suggest a possible role of peripheral benzodiazepine receptors in the organism response to tissue damage associated with **inflammatory** mediator production.

L7 ANSWER 16 OF 66 MEDLINE on STN
AN 2002095153 MEDLINE
DN 21682472 PubMed ID: 11824844
TI Hippocampal damage mediated by corticosteroids--a neuropsychiatric research challenge.
AU Hoschl C; Hajek T
CS Prague Psychiatric Centre, Czech Republic.. hoschl@pcp.lf3.cuni.cz
SO EUROPEAN ARCHIVES OF PSYCHIATRY AND CLINICAL NEUROSCIENCE, (2001) 251 Suppl 2 II81-8. Ref: 63
Journal code: 9103030. ISSN: 0940-1334.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200207
ED Entered STN: 20020205
Last Updated on STN: 20020718
Entered Medline: 20020717
AB There is an increasing evidence that corticosteroids damage the

hippocampus in rodents and in primates. Hippocampal atrophy induced by corticosteroids may play an important role in the pathogenesis of a range of neuropsychiatric disorders. Hippocampus is necessary for short-term memory consolidation and HPA axis regulation. Signs of hippocampal damage (HPA dysregulation in combination with memory impairment) are found in affective disorders, Alzheimer's disease and in posttraumatic stress disorder. MRI volumetry reveals reduced hippocampal volume in these diseases. Evidence supporting the "glucocorticoid hypothesis" of psychiatric disorders is reviewed in the first part of the paper. Unresolved questions concerning temporary aspects of neurodegeneration, causality, reversibility, type of damage, factors increasing hippocampal vulnerability, and both pharmacological (CRH antagonists, antiglucocorticoid drugs, **GABA**-ergic, serotonergic, glutamatergic agents) and non-pharmacological (psychotherapy) **treatment** approaches are discussed in the second part.

L7 ANSWER 17 OF 66 MEDLINE on STN
AN 2002068672 MEDLINE
DN 21653423 PubMed ID: 11793144
TI [Pathophysiology of low back pain and the transition to the chronic state - experimental data and new concepts].
Pathophysiologie des Ruckenschmerzes und seine Chronifizierung - Tierexperimentelle Daten und neue Konzepte.
AU Mense S
CS Institut fur Anatomie und Zellbiologie III, Klinikum der Universitat Heidelberg.. mense@urz.uni-heidelberg.de
SO Schmerz, (2001 Dec) 15 (6) 413-7.
Journal code: 8906258. ISSN: 0932-433X.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA German
FS Priority Journals
EM 200202
ED Entered STN: 20020125
Last Updated on STN: 20020223
Entered Medline: 20020222
AB The present article concentrates on mechanisms that lead to the excitation of nociceptors in soft tissues and nociceptive neurones in the spinal dorsal horn. These mechanisms may contribute to the so-called unspecific low back pain. Properties of nociceptors in soft tissues: A nociceptive ending in soft tissue contains a multitude of receptor molecules in its membrane. The molecular receptors include binding sites for algesic substances that are released during painful stimulation or pathologic alterations of the tissue: bradykinin (BK), serotonin (5-HT), prostaglandin E2 (PG E2), adenosine triphosphate (ATP) and protons (H(+)). The excitation and sensitisation of nociceptors by these substances can be explained by the binding of the substances to the receptor molecules in the membrane of the receptive ending and ensuing opening of ion channels or activation of metabolic cascades. Purinergic receptor molecules in the membrane of nociceptors are activated by ATP. These receptors may be of particular importance for deep somatic pain, because ATP is present in large amounts in muscle tissue and is released during muscle damage. ATP-sensitive nociceptors appear to be distinct from nociceptors that can be excited by protons. The conduction of nociceptive information from muscle to the spinal cord is partly carried by unmyelinated fibres that possess tetrodotoxin-resistant (TTX-r) Na(+)-channels. Therefore, a drug that specifically blocks TTX-r Na(+)-channels would be a new attractive tool in the **treatment** of patients with deep somatic pain.
Chronic muscle lesions such as a myositis have been shown to be associated with a higher innervation density of the tissue with free nerve endings that contain the neuropeptide substance P (SP). Many of these endings are likely to be nociceptors. Since a painful stimulus that acts on a muscle with increased nociceptor density will excite more nociceptors and elicit more pain, the increase in nociceptor density constitutes a peripheral mechanism for hyperalgesia. In muscle free nerve endings - many of which are nociceptive - the neuropeptides SP, calcitonin gene-related peptide (CGRP) and somatostatin have been shown to be present. These substances are released from the receptive endings in muscle when they are stimulated. SP and CGRP have a strong effect on blood vessels and induce

local vasodilatation and oedema. The local oedema in the vicinity of the nociceptor is associated with the release of BK from plasma proteins, which increases the excitability of the nerve ending (see below). Thus, a local vicious cycle forms that may contribute to the formation of trigger points. Sensitisation of nociceptors and peripheral hyperalgesia: Nociceptors are easily sensitised, i.e. following a conditioning stimulus they are more sensitive to the unconditioned stimulus. In animals and humans, the responses to injections of BK can be increased by 5-HT or PG E2. The responses of muscle nociceptors to mechanical stimuli are likewise enhanced after administration of BK. During overuse, ischemia or **inflammation** of soft tissues, the tissue concentrations of BK, PG E2, and 5-HT are elevated and sensitise muscle nociceptors. A sensitised nociceptor is excited and elicits pain when innocuous mechanical stimuli act on the muscle, e.g. during contractions or stretch. Therefore, in chronically altered soft tissues, weak everyday stimuli are likely to cause pain. Mechanisms at the spinal level: In experiments on rats in which a myositis of the gastrocnemius-soleus (GS) muscle was induced experimentally, the effects of a peripheral painful lesion on the discharge behaviour of sensory dorsal horn neurones were studied. One of the main effects of the myositis was an expansion of the input (target) region of the muscle nerve, i.e. the population of dorsal horn neurones responding to an electrical standard stimulus applied to the GS muscle nerve grew larger. One reason for the myositis-induced expansion of the input region is hyperexcitability of the neurones caused by the release of SP and glutamate from the spinal terminals of muscle afferents with ensuing activation of NMDA channels in dorsal horn neurones (central sensitisation). The central sensitisation is of clinical importance because it can explain the hyperalgesia and spread of pain in patients. In contrast to excitability, the resting activity of dorsal horn neurones - which is likely to induce spontaneous pain in patients - does not appear to depend on the release of SP and glutamate but on the concentration of nitric oxide (NO) in the spinal cord. A pharmacological block of the NO synthesis led to a significant increase in background activity without affecting the excitability of the dorsal horn neurones. Such an increase in background activity was observed exclusively in nociceptive neurones, i.e. a local lack of NO in the spinal cord induces spontaneous pain. According to data from animal experiments, a decrease in the spinal NO concentration occurs as a sequel of a chronic muscle lesion; therefore, a lack of NO is a probable factor for the induction of chronic spontaneous pain. Normally, lesion-induced pain subsides and does not develop into chronic pain. The mechanisms governing the return to normal neuronal behaviour after a peripheral lesion are not well studied. Probably, the activation of inhibitory mechanisms, e.g. increased spinal synthesis of **GABA** or elevated activity of the descending antinociceptive system contribute to the restoration of normal function. The final step in the transition from acute to chronic pain are structural changes that perpetuate the functional changes. In the rat myositis model, an increase in the number of synapses on the surface of NO-snythesizing cells was present 8 h following induction of the myositis. These data show that structural changes appear quite early in the development of a painful disorder. A novel hypothesis for the development of chronic pain states that a strong nociceptive input to the spinal cord leads to cell death predominantly in inhibitory interneurones. Most of these interneurones are assumed to be tonically active; when their number decreases, the nociceptive neurones are chronically disinhibited and elicit continuous pain also in the absence of a noxious stimulus.

L7 ANSWER 18 OF 66 MEDLINE on STN
AN 2002014914 MEDLINE
DN 21310410 PubMed ID: 11417852
TI Reduction of acute **inflammation** in rats by diazepam: role of peripheral benzodiazepine receptors and corticosterone.
AU Lazzarini R; Malucelli B E; Palermo-Neto J
CS Laboratory of Applied Pharmacology and Toxicology, School of Veterinary Medicine, University of Sao Paulo, Brazil.
SO IMMUNOPHARMACOLOGY AND IMMUNOTOXICOLOGY, (2001 May) 23 (2) 253-65. Journal code: 8800150. ISSN: 0892-3973.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals
EM 200112
ED Entered STN: 20020121
Last Updated on STN: 20020121
Entered Medline: 20011207
AB Carrageenin causes a reproducible **inflammatory** reaction and remains the standard irritant for examining acute **inflammation** and anti-**inflammatory** drugs. High doses of diazepam (10.0-20.0 mg/Kg) were shown to reduce the volume of acute **inflammatory** paw edema in rats as a response to carrageenin administration. The present experiment was undertaken to investigate the possible roles of peripheral-type benzodiazepine receptors (PBRs) and corticosterone on the anti-**inflammatory** effects of diazepam. Five experiments were conducted to assess the effects of a single dose (10.0 mg/Kg) of diazepam on carrageenin-induced paw edema (CIPE), pleurisy and increase in vascular permeability in rats. Results showed that: 1. diazepam or Ro5-4864 (a PBR agonist) **treatment** reduced CIPE values; 2. prior **treatment** with PK11195 (a non-benzodiazepine PBR antagonist) suppressed the effects of either diazepam or Ro5-4864 on CIPE; 3. diazepam reduced the volume of the pleural exudate in carrageenin-injected rats, as well as its leukocyte count; 4. diazepam **treatment** reduced the magnitude of the increase in vascular permeability caused by carrageenin; 5. adrenalectomy suppressed the effects of diazepam on CIPE; and 6. diazepam **treatment** increased the serum concentration of corticosterone. These results suggest a relevant role of PBR and corticosterone on diazepam-induced changes in **inflammation**. They are discussed in the light of a possible activation of mitochondrial PBRs within the adrenal gland cells by diazepam, thereby increasing the serum levels of corticosterone and thus reducing CIPE.

L7 ANSWER 19 OF 66 MEDLINE on STN
AN 2001686226 MEDLINE
DN 21589317 PubMed ID: 11732703
TI Effects of pre- and postnatal corticosterone exposure on the rat hippocampal **GABA** system.
AU Stone D J; Walsh J P; Sebro R; Stevens R; Pantazopolous H; Benes F M
CS Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, USA.
NC MH 00432 (NIMH)
MH 31154 (NIMH)
MH 42261 (NIMH)
SO HIPPOCAMPUS, (2001) 11 (5) 492-507.
Journal code: 9108167. ISSN: 1050-9631.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200205
ED Entered STN: 20011205
Last Updated on STN: 20020508
Entered Medline: 20020507
AB Several lines of evidence have implicated prenatal stress and the hippocampal **GABA** system in the pathophysiology of schizophrenia, and prenatal stress is believed to increase the risk for schizophrenia through alterations of this neurotransmitter. To explore this hypothesis, we **treated** male rats pre- and/or postnatally (P48 and P60) with either corticosterone (CORT) or vehicle to establish three study groups: VVV, receiving vehicle at all three time points; VCC, receiving vehicle prenatally and CORT at both postnatal timepoints; and CCC, receiving CORT at all three timepoints. Animals were sacrificed at either 24 h or 5 days after final injection and examined for mRNA levels of GAD65, GAD67, and the **GABA**(A) receptor subunits alpha2 and gamma2. At 24 h, GAD65 mRNA was decreased in CA1, CA2, CA4, and dentate gyrus (DG) of VCC rats; this effect was either decreased or reversed in CCC-**treated** animals. No effect was detected in GAD67 mRNA at 24 h. At 5 days, CORT **treatment** increased GAD67 mRNA levels in CA1, CA3, and DG. Prenatal **treatment** with CORT was associated with increased responsiveness only in CA3 and DG. For the GABAA receptor, alpha2 subunit

mRNA did not show any change in response to CORT **treatment**, while that for the gamma2 subunit was decreased in CA2 of both VCC- and CCC-**treated** animals. Consistent with gamma2 subunit mRNA decreases, benzodiazepine (BZ) receptor binding activity was decreased in CA2 with CORT **treatment**. Prenatal CORT exposure neither increased nor decreased this effect. These results demonstrate that CORT administration is associated with a complex regulation of mRNA expression for pre- and postnatal aspects of the hippocampal **GABA** system. Under these conditions, prenatal exposure to CORT may sensitize some of these effects, but does not fundamentally alter the nature of this response.

L7 ANSWER 20 OF 66 MEDLINE on STN
AN 2001683955 MEDLINE
DN 21586961 PubMed ID: 11729541
TI Weight gain in post-seized rats is facilitated by adding aspirin, glucose, or glucose-taurine-acetaminophen to food mush.
AU Jedrzejko C; Persinger M A
CS Laurentian University, Sudbury, Ontario.
SO PSYCHOLOGICAL REPORTS, (2001 Aug) 89 (1) 188-90.
Journal code: 0376475. ISSN: 0033-2941.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200201
ED Entered STN: 20011204
Last Updated on STN: 20020124
Entered Medline: 20020102
AB Adult male rats were seized with lithium and pilocarpine and administered acepromazine to facilitate survival. After four days (1) 8 mg of acetylsalicylic acid (aspirin), (2) 100 mg taurine-15 mg acetaminophen (Tylenol)-40 mg glucose, (3) 40 mg glucose, or (4) water was added to the food mush daily for 30 days. A fifth group served as non-seized controls. Within one week all pharmacological **treatments** promoted more weight recovery than food mush only. The rats receiving aspirin (equivalent to 3 tablets/day for humans) showed the greatest early recovery. After 15 days of **treatment** the pharmacologically **treated** seized rats had returned to baseline weight and did not differ from normals whereas seized rats given only food mush had not. We suggest inhibiting prostaglandins by anti-**inflammatory** compounds or stimulating the **GABA** shunt pathway through enhanced dietary glucose to accelerate weight gain following the significant loss that accompanies brain injury.

L7 ANSWER 21 OF 66 MEDLINE on STN
AN 2001669497 MEDLINE
DN 21568476 PubMed ID: 11711865
TI Spinal **GABA**(B)-receptor antagonism increases nociceptive transmission in vivo.
AU Sokal D M; Chapman V
CS School of Biomedical Sciences, E Floor, Medical School, University of Nottingham, Nottingham NG7 2UH, UK.
SO NEUROREPORT, (2001 Oct 29) 12 (15) 3247-50.
Journal code: 9100935. ISSN: 0959-4965.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200202
ED Entered STN: 20011122
Last Updated on STN: 20020220
Entered Medline: 20020219
AB **GABA**(B) receptors modulate primary afferent fibre evoked responses of spinal neurones. Here effects of the selective **GABA** (B) receptor antagonist, CGP-35348, on electrically-evoked responses of spinal neurones in control and carrageenan-**inflamed** rats were studied. Spinal CGP-35348 (0.1-10 microg/50 microl) did not alter Abeta- or Adelta-fibre evoked neuronal responses in control rats, although

C-fibre evoked responses and post discharge responses of spinal neurones were significantly facilitated by 3.0 and 10.0 microg/50 microl CGP-35348 ($p < 0.05$). In carrageenan-**treated** animals, spinal CGP-35348 did not alter electrically evoked responses of spinal neurones at any dose. Our data suggest that following acute peripheral **inflammation** there is loss of endogenous **GABA**(B) receptor mediated inhibition of C-fibre transmission at the level of the spinal cord.

L7 ANSWER 22 OF 66 MEDLINE on STN
AN 2001541940 MEDLINE
DN 21474027 PubMed ID: 11589720
TI Prevalence and risk of gingival enlargement in patients **treated** with anticonvulsant drugs.
AU Brunet L; Miranda J; Roset P; Berini L; Farre M; Mendieta C
CS Periodontics Unit, Universitat de Barcelona, Barcelona, Spain.
SO EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, (2001 Sep) 31 (9) 781-8.
Journal code: 0245331. ISSN: 0014-2972.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200112
ED Entered STN: 20011009
Last Updated on STN: 20020122
Entered Medline: 20011207
AB BACKGROUND: Predictors of gingival enlargement in patients **treated** with anti-epileptics have not been previously assessed. This study was conducted to determine, with the aid of two indices that score vertical and horizontal overgrowth, the prevalence and risk factors for gingival enlargement in patients **treated** with phenytoin and other anticonvulsant drugs. MATERIALS AND METHODS: A cross-sectional study was conducted and data from 59 patients taking antiepileptics were compared with 98 controls. Gingival enlargement was evaluated with two indices to score vertical overgrowth [Gingival overgrowth index (GO] and horizontal overgrowth [Miranda-Brunet index (MB)]. Gingival index, plaque index, and probing depth were also evaluated. RESULTS: The prevalence of gingival enlargement was significantly higher ($P < 0.0001$) for both indices in the anticonvulsants **treated** groups than in the control group. Gingival overgrowth was significantly higher for both indices in the phenytoin group than in the non phenytoin group. Among the possible risk factors, only the gingival index showed a significant association with gingival enlargement. For the MB index the risk of gingival enlargement (odds ratio) associated to phenytoin therapy and other anticonvulsants therapy were 52.6 (13.5-205) and 6.6 (1.5-28.2). Gingival index-adjusted odds ratios for the same drugs were 5.7 (1.3-24.7) and 18.1 (2-158), respectively. The concordance between GO and MB indices in the control group and in the phenytoin-group and non phenytoin-group showed a Kappa value of 0.773 and 0.697, respectively. CONCLUSION: This study reports significant differences in the prevalence and severity of gingival overgrowth in two groups of patients, one **treated** with phenytoin, and another **treated** with other anticonvulsants. Gingival **inflammation** is a significant risk factor for gingival enlargement in these patients.

L7 ANSWER 23 OF 66 MEDLINE on STN
AN 2001461179 MEDLINE
DN 21396979 PubMed ID: 11506187
TI Melatonin enhances Th2 cell mediated immune responses: lack of sensitivity to reversal by naltrexone or benzodiazepine receptor antagonists.
AU Raghavendra V; Singh V; Kulkarni S K; Agrewala J N
CS Immunology Laboratory, Institute of Microbial Technology, Chandigarh, India.
SO MOLECULAR AND CELLULAR BIOCHEMISTRY, (2001 May) 221 (1-2) 57-62.
Journal code: 0364456. ISSN: 0300-8177.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 200202
ED Entered STN: 20010820
Last Updated on STN: 20020216
Entered Medline: 20020215
AB Chronic administration of melatonin for 5 days to antigen-primed mice increased the production of pro-**inflammatory** cytokine IL-10 but decreased the secretion of anti-**inflammatory** cytokine TNF-alpha. These results further confirm that melatonin activates Th2-like immune response. Whether melatonin-mediated Th2 response is dependent on opioid or central and peripheral benzodiazepine receptors was also examined. Hence, melatonin was administered to antigen-sensitised mice with either naltrexone (a mu opioid receptor antagonist) or flumazenil (a central benzodiazepine receptor antagonist) or PK11195 (a peripheral benzoidiazepine receptor antagonist). No significant difference in melatonin-induced Th2 cell response was observed by naltrexone, flumazenil or PK11195 **treatment**. These findings suggest that the Th2 cell response induced by melatonin in antigen sensitised mice neither dependent on endogenous opioid system nor is modulated through the central or peripheral benzodiazepine receptors.

L7 ANSWER 24 OF 66 MEDLINE on STN
AN 2001442670 MEDLINE
DN 21380623 PubMed ID: 11488432
TI Involvement of GABAergic systems in manifestation of pharmacological activity of desipramine.
AU Asahi Y; Yonehara N
CS Bobath Memorial Hospital, Osaka, Japan.
SO JAPANESE JOURNAL OF PHARMACOLOGY, (2001 Jul) 86 (3) 316-22.
Journal code: 2983305R. ISSN: 0021-5198.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200201
ED Entered STN: 20010813
Last Updated on STN: 20020124
Entered Medline: 20020102
AB We have conducted this study to elucidate the influence of GABAergic systems on manifestation of pharmacological activity of desipramine using both pharmacological and electrophysiological methods. Desipramine (20 mg/kg, i.p.) significantly blocked the adjuvant-induced thermal hyperalgesia, which was facilitated by **treatment** with the **GABA**(A) antagonist picrotoxin (2 mg/kg, i.p.) or the **GABA** (B) antagonist saclofen (2 mg/kg, i.p.). This analgesic effect of desipramine was antagonized by post-**treatment** with picrotoxin or saclofen. However, none of these compounds showed any effect in normal animals without adjuvant-induced **inflammation**. In a slice preparation of the hippocampus, **treatment** with **GABA** (10(-5)-5 x 10(-4) M), baclofen (10(-5)-10(-4) M) or muscimol (10(-5)-10(-4) M) inhibited the field potential evoked in pyramidal neurons by Schaffer collateral stimulation. The inhibitory effect of **GABA** was facilitated by concurrent application of desipramine, carbamazepine or diazepam at a concentration of 5 x 10(-5)-2 x 10(-4) M. The rank of order of facilitation is: desipramine > carbamazepine > diazepam. Desipramine also enhanced the inhibitory effect of baclofen and muscimol. These results suggest that desipramine causes GABAergic systems to activate still more, and this phenomenon appears to be involved in manifestation of the pharmacological activity of desipramine such as antinociception.

L7 ANSWER 25 OF 66 MEDLINE on STN
AN 2001307113 MEDLINE
DN 21186917 PubMed ID: 11291022
TI Approaches to memory loss in neuropsychiatric disorders.
AU Devi G; Silver J
CS New York Memory and Health Aging Services, Department of Medicine, Division of Neurology, Lenox Hill Hospital, 65 East 76th Street, New York, NY 10021, USA.. Gd@nymemory.org
SO SEMINARS IN CLINICAL NEUROPSYCHIATRY, (2000 Oct) 5 (4) 259-65. Ref: 32

Journal code: 9604647. ISSN: 1084-3612.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200105
ED Entered STN: 20010604
Last Updated on STN: 20010604
Entered Medline: 20010531
AB Many neuropsychiatric disorders affect memory. Brain regions important in the neuroanatomic substrate of memory include the hippocampus, and sections of the frontal, temporal, and parietal cortices and the thalamus. Acetylcholine and many other neurotransmitters and neuromodulators including dopamine, glutamate, **GABA**, the catecholamines, and estrogen modulate cognitive function. **Treatment** approaches to memory loss typically use Alzheimer's dementia as the template, and are discussed in this report.

L7 ANSWER 26 OF 66 MEDLINE on STN
AN 2001257985 MEDLINE
DN 21095538 PubMed ID: 11166695
TI Effects of baclofen on colon **inflammation**-induced Fos, CGRP and SP expression in spinal cord and brainstem.
AU Lu Y; Westlund K N
CS Department of Anatomy and Neuroscience and The Marine Biomedical Institute, The University of Texas Medical Branch at Galveston, Galveston, TX 77555-1069, USA.
NC NS11255 (NINDS)
RO1 NS32778 (NINDS)
SO BRAIN RESEARCH, (2001 Jan 19) 889 (1-2) 118-30.
Journal code: 0045503. ISSN: 0006-8993.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200105
ED Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517
AB The present study demonstrates sites of expression for Fos protein in the brainstem and lumbosacral spinal cord of rats subjected to mustard oil irritation of the colon. The protective effect of baclofen, a selective **GABA**(B) receptor agonist, on the induced Fos protein increases was determined. Mustard oil injected into the lumen of the colon produces an acute site-specific **inflammation**. Immunocytochemical localization of Fos protein in neuronal nuclei was evident after 1 h, was greatest at 2 h and was still evident but declining at 8 h. In the spinal cord the majority of Fos labeled neurons were localized in the superficial laminae of lumbar (L6) cord with more found in the sacral (S1) cord. Some labeled neurons were also found in the deeper spinal laminae, intermediolateral nucleus and around lamina X. Brainstem sites expressing Fos included the nucleus of the solitary tract in the medulla, parabrachial, locus coeruleus, pontine and caudal dorsal raphe nuclei and periaqueductal gray. Weak Fos protein labeling existed in a few cells in vehicle control animals. Systemic administration of the **GABA**(B) receptor agonist, baclofen (10 mg/kg, i.p.), significantly reduced Fos expression in the spinal cord after mustard oil **treatment** but significantly increased the relative number of nuclei labeled in the nucleus of the solitary tract. Baclofen also significantly decreases dorsal horn CGRP immunoreactivity relative to the increased levels seen after **inflammation** of the colon. The SP content increases observed after **inflammation** of the colon were not altered by baclofen. These data suggest that: (1) neurons in regions important for nociceptive transmission, descending inhibitory control and autonomic control are activated by noxious stimulation of the colon, and (2) baclofen specifically reduces Fos expression in the superficial dorsal

horn of the spinal cord induced by nociceptive afferent input.

L7 ANSWER 27 OF 66 MEDLINE on STN
AN 2001176794 MEDLINE
DN 21026764 PubMed ID: 11153899
TI Physiopathology of symptomatic and latent forms of central nervous hyperexcitability due to magnesium deficiency: a current general scheme.
AU Durlach J; Bac P; Bara M; Guiet-Bara A
CS SDRM, H pital Saint-Vincent-de-Paul, Paris, France.
SO MAGNESIUM RESEARCH, (2000 Dec) 13 (4) 293-302. Ref: 64
Journal code: 8900948. ISSN: 0953-1424.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200103
ED Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329
AB Symptomatic forms of central nervous hyperexcitability (NHE) due to magnesium deficiency results from the sum of direct cellular effects and of local and systemic mediated effects inducing depolarization and NHE. Direct effects associate decreased energy and cationic gradient with disturbances in Ca distribution, decreased second messenger nucleotidic ratio and increased susceptibility to peroxidation. Local mediated effects associate increased activity of excitatory neuromediators: acetylcholine, catecholamines and ionotropic - (NMDA and non-NMDA) - receptors of excitatory aminoacids (EAA), with decreased activity of inhibitory neuromediators: **GABA**, taurine, glutaurine, adenosine and K receptors of opioids. Systemic mediated effects associate increased production of **inflammatory** mediators: neuropeptides, prostanoids, cytokines Th 1, aldehydes with decreased activity of oxidant and antialdehyde defences. Compensatory factors instrumental in the latency of NHE due to magnesium deficiency may also be direct or mediated. Increased intracellular pH, modifications of Ca and Mg binding proteins, increase in 'magnesium-like' polyamines, stimulation of cellular antioxidant system; decreased activity of EAA metabotropic receptors and of opioid mu (and delta) receptors, increased activity of inhibitory neuromediators, increased production of anti-**inflammatory** mediator such as cytokines Th 2, stimulation of systemic antioxidant and antialdehyde defences. A lot of diverse compounds are able to palliate symptomatic NHE due to magnesium deficiency either by pharmacodynamic effects or through physiopathological intervention. The efficiency of these **treatments** can be evaluated on multiple disparate parameters. The pattern of NHE due to magnesium deficiency differs according to species, strains, gender, age and intensity of magnesium deficiency. For example: hot plate test showed a hypoalgesia 'morphine-like' pattern induced by magnesium deficiency cured by magnesium acetyltaurinate in mice whilst paw pressure test showed a hyperalgic pattern caused by magnesium deficiency cured by dizolcipine in rats. Now it seems difficult to rank hierarchically the various physiopathological mechanisms of NHE due to magnesium deficiency. But the proposed general scheme of the factors controlling this NHE provides a possible explanation of both diffuse symptomatic and latent forms and stresses the complexity of the physiopathological mechanisms of central NHE due to magnesium deficiency.

L7 ANSWER 28 OF 66 MEDLINE on STN
AN 2001129313 MEDLINE
DN 21019424 PubMed ID: 11132509
TI Comparative pharmacokinetics of submucosal vs. intravenous flumazenil (Romazicon) in an animal model.
AU Oliver F M; Sweatman T W; Unkel J H; Kahn M A; Randolph M M; Arheart K L; Mandrell T D
CS University of Tennessee, USA.
SO PEDIATRIC DENTISTRY, (2000 Nov-Dec) 22 (6) 489-93.
Journal code: 7909102. ISSN: 0164-1263.

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Dental Journals; Priority Journals
EM 200103
ED Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010301
AB PURPOSE: This study was performed to determine the bioavailability and local tissue toxicological safety of flumazenil (Romazicon) when administered by oral submucosal (SM) as opposed to intravenous (i.v.) injection. METHODS: Six dogs each received SM flumazenil (0.2 mg), and their serum was collected at predetermined time intervals (0-2 h) and frozen (-70 degrees C). Seven days later, the dogs received an identical dose of i.v. flumazenil, and serum samples were again collected, as above. Comparative quantitation of flumazenil levels (i.v. vs. SM) was made using a sensitive HPLC assay (UV detection). Direct/local drug toxicity was visually scored by unbiased raters of color photographs (test and control mucosa) taken at 1, 2, and 7 days following SM flumazenil injection. An oral pathologist examined slides processed from control and **treatment** tissues (hematoxylin and eosin staining) taken (punch biopsy) 1 week following SM injection to compare with direct clinical scores. RESULTS: Serum flumazenil levels reached a plateau (8.5 +/- 1.5 ng/mL, mean +/- SD) within 4 min of SM drug injection and declined thereafter to -2 ng/mL by 2 h. Bioavailability of SM flumazenil was 101 +/- 14%, based upon measuring the area under the serum concentration-time curves over 1.5 h (AUC 0-1.5 h, SM vs. i.v. drug). Thus, serum drug levels following SM drug administration were broadly comparable to those obtained during the elimination phase of corresponding i.v. drug delivery. Regarding drug tissue toxicity, no evidence of direct drug toxicity was observed by unbiased raters of color photographs (test and control mucosa) taken at 1, 2, and 7 days following SM flumazenil injection. Following pathologic review, no difference was seen in the degree of **inflammation** between **treatment** and control tissue. CONCLUSION: At the quantity and concentration used, SM drug flumazenil administration appears to be both a safe and a viable alternative to bolus i.v. drug delivery and worthy of further investigation.

L7 ANSWER 29 OF 66 MEDLINE on STN
AN 2001110848 MEDLINE
DN 20553610 PubMed ID: 11099825
TI Antinociceptive effect of a group II metabotropic glutamate receptor antagonist in the thalamus of monoarthritic rats.
AU Neto F L; Castro-Lopes J M
CS Institute of Histology and Embryology and IBMC, Faculty of Medicine of Oporto, 4200-319, Porto, Portugal.
SO NEUROSCIENCE LETTERS, (2000 Dec 15) 296 (1) 25-8.
Journal code: 7600130. ISSN: 0304-3940.
CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200102
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010202
AB Adult rats were rendered monoarthritic (MA) by injection of 50 microl of complete Freund's adjuvant (CFA) into the tibiotarsal joint. The ankle-bend (AB) test of nociception was performed in those animals before and during 60 min after the stereotaxic injection of 2 microl of either saline (controls) or (2S)-alpha-ethylglutamic acid (EGLU, 80 nmol in 2 microl), a group II metabotropic glutamate receptors (mGluR) antagonist, in the reticular thalamic nucleus (Rt) contralateral to the arthritic joint. AB scores reached near maximum values before the stereotaxic injections (18.7+/-0.8), and remained constant throughout the entire experimental period in the control group, denoting marked allodynia. In the EGLU-**treated** group, AB scores gradually decreased after EGLU injection, with minimum values at 10 min (7.7+/-1.6), recovering to scores near maximum at 60 min (19.7+/-0.3). The data point to an activation of

group II mGluR by noxious inputs in the Rt of MA rats, suggesting their participation in inhibiting local gamma-aminobutyric acid (**GABA**)ergic inhibitory neurones.

L7 ANSWER 30 OF 66 MEDLINE on STN
AN 2001067525 MEDLINE
DN 20534784 PubMed ID: 11080527
TI Anti-**inflammatory** effects of peripheral benzodiazepine receptor ligands in two mouse models of **inflammation**.
AU Torres S R; Frode T S; Nardi G M; Vita N; Reeb R; Ferrara P; Ribeiro-do-Valle R M; Farges R C
CS Department of Pharmacology, Centre of Biological Sciences, Universidade Federal de Santa Catarina, Rua Ferreira Lima, 82, SC, 88015-420, Florianopolis, Brazil.
SO EUROPEAN JOURNAL OF PHARMACOLOGY, (2000 Nov 17) 408 (2) 199-211. Journal code: 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200012
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001227
AB In vivo **treatment** of mice with peripheral benzodiazepine receptor ligands exerts an inhibitory effect on the **inflammatory** response in two models of acute **inflammation**. In the first model, pretreatment of the animals (24 h) with 1-(2-chlorophenyl)-N-methyl-N(1-methylpropyl)-3-isoquinoline carboxamide (PK11195) and 7-chloro-5-(4-Chlorophenyl)-1, 3-dihydro-1-methyl-2-H-1,4-benzodiazepin-2 (Ro5-4864), at different doses (0.00001-10 mg/kg, i.p.) dose dependently inhibited the formation of mouse paw oedema induced by carrageenan with mean ID(50s) of 0.009 (95% confidence limits=0.0076-0.013) and 0.04 (95% confidence limits=0.025-0.0086) mg/kg, respectively. Both ligands (0. 1 mg/kg, i.p.) inhibited in the same way the mouse paw oedema induced by carrageenan in animals with and without adrenal glands. PK11195 and Ro5-4864 (0.1 mg/kg, i.p.) inhibited the mouse paw oedema induced by several **inflammatory** mediators. In the second model, the pretreatment (24 h) with peripheral benzodiazepine receptor ligands (0.1 mg/kg, i.p.) exerted an inhibitory effect on neutrophil influx and produce a marked inhibition of carrageenan-produced interleukin-13 and interleukin-6 in pleural exudation. Our results extend previous findings that peripheral benzodiazepine receptor is involved in the **inflammatory** response, and suggest that this action may be linked to the action of different **inflammatory** mediators, probably mainly by the inhibition of the release of pro-**inflammatory** cytokines.

L7 ANSWER 31 OF 66 MEDLINE on STN
AN 2001035411 MEDLINE
DN 20535473 PubMed ID: 11082887
TI [Antisense targeting in neurology]. Antisense targeting en Neurologia.
AU Telleria-Diaz A
CS Unidad de Cuidados Intermedios, Hospital General Docente Enrique Cabrera, La Habana, Cuba.. diaz@mti-n.uni-jena.de
SO REVISTA DE NEUROLOGIA, (2000 Oct 16-31) 31 (8) 762-9. Ref: 83 Journal code: 7706841. ISSN: 0210-0010.
CY Spain
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA Spanish
FS Priority Journals
EM 200011
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001130
AB INTRODUCTION: Antisense targeting refers to the use of synthetic short

lengths of single stranded DNA, or RNA with base sequences complementary to a specific gene or its mRNA. Commonly, synthetic oligonucleotides are designed to hybridize to specific mRNA and thus preventing its translation in a specific protein. DEVELOPMENT: The use of this technology as research tool is well known since two decades ago, but it has been in the last few years, when it has been proposed as a promising tool for the development of a new generation of drugs with high specificity, relative ease of production and low rate of toxicity. Antisense therapeutics is currently being evaluated in clinical trials for cancer, **inflammation**, and viral diseases. In the field of Neuropharmacology, it has become in a very valuable tool to block the expression of specific genes in vitro as well in the living brain. In this article, we review the contributions of this technology in the field of the Neurosciences, and also give an overview concerning the advances of the antisense strategy in the design of possible new **treatments** for certain neurological disorders. Other clinically relevant information regarding molecular biology, pharmacokinetics, mechanism of action, and side effects of antisense oligonucleotides has been collected and summarized. CONCLUSIONS: In the neuropharmacological area is the Neurooncology the most intensively researched; nevertheless, the lack of oligos that cross the blood-brain barrier in sufficient amount continues being one of the main difficulties for the successful application of this technique on the central nervous system.

L7 ANSWER 32 OF 66 MEDLINE on STN
AN 2000483006 MEDLINE
DN 20453325 PubMed ID: 10996212
TI Increased peripheral benzodiazepine binding sites and pentraxin 3 expression in the spinal cord during EAE: relation to **inflammatory** cytokines and modulation by dexamethasone and rolipram.
AU Agnello D; Carvelli L; Muzio V; Villa P; Bottazzi B; Polentarutti N; Mennini T; Mantovani A; Ghezzi P
CS 'Mario Negri' Institute for Pharmacological Research, Milano, Italy.
SO JOURNAL OF NEUROIMMUNOLOGY, (2000 Sep 22) 109 (2) 105-11.
Journal code: 8109498. ISSN: 0165-5728.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200010
ED Entered STN: 20001019
Last Updated on STN: 20001019
Entered Medline: 20001012
AB We have studied the mRNA expression of pentraxin 3 (PTX3) and the binding of the peripheral-type benzodiazepine receptor (PBR) ligand, [3H]-PK11195, in the spinal cord of Lewis rats where EAE was actively induced. PTX3 was induced during the active phase of EAE (day 10-14), it remained high up to 30 days and disappeared only 60 days later. Similarly, PK11195 binding peaked at day 14-17 during the recovery and it disappeared by day 60. On the other hand, the levels of TNF and IL-6 in the spinal cord were elevated at the peak and at the onset of clinical signs and returned to non-detectable by day 14-17. Dexamethasone abolished all these changes, while **treatment** with rolipram, delayed the appearance of the disease and then decreased its severity. However the peaks of TNF, IL-6, PBR and PTX3 levels in spinal cord were only delayed, but not reduced, by rolipram **treatment**. In conclusion, we show two types of **inflammatory** changes in EAE: acute, short term changes (TNF and IL-6), that correlate with the disease; and effects such as PTX3 expression and PK11195 binding that last longer after recovery from the disease.

L7 ANSWER 33 OF 66 MEDLINE on STN
AN 2000363333 MEDLINE
DN 20363333 PubMed ID: 10908041
TI Neuroprotective agent chlomethiazole attenuates c-fos, c-jun, and AP-1 activation through inhibition of p38 MAP kinase.
AU Simi A; Ingelman-Sundberg M; Tindberg N
CS Division of Molecular Toxicology, National Institute for Environmental Medicine, Stockholm, Sweden.

SO JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM, (2000 Jul) 20 (7) 1077-88.
Journal code: 8112566. ISSN: 0271-678X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200008
ED Entered STN: 20000811
Last Updated on STN: 20000811
Entered Medline: 20000803
AB Recent evidence suggests that stress-activated protein kinases expressed in glial cells have very important roles during cerebral ischemia. The neuroprotective agent chlomethiazole, which is known to enhance the conductance at the **GABA**(A) receptor complex, is presently in clinical trials for the **treatment** of severe stroke. Here the authors suggested that chlormethiazole has anti-**inflammatory** properties because it potently and selectively inhibited p38 mitogen-activated protein (MAP) kinase in primary cortical glial cultures. The inhibition of p38 MAP kinase resulted in the attenuation of the induction of c-fos and c-jun mRNA and AP-1 DNA binding by lipopolysaccharide (LPS). In addition, chlomethiazole inhibited the activation of an AP-1-dependent luciferase reporter plasmid in SK-N-MC human neuroblastoma cells in response to glutamate. Chlomethiazole inhibited the p38 MAP kinase activity as revealed by the decrease in the LPS-induced phosphorylation of the substrates ATF-2 and hsp27, whereas the phosphorylation status of the p38 MAP kinase itself was unaffected. Interestingly, chlomethiazole exhibited an IC(50) of approximately 2 micromol/L for inhibition of c-fos mRNA expression, indicating 25 to 75 times higher potency than reported EC(50) values for enhancing **GABA**(A) chloride currents. The results indicated a novel mechanism of action of chlomethiazole, and provided support for a distinctive role of p38 MAP kinase in cerebral ischemia.

L7 ANSWER 34 OF 66 MEDLINE on STN
AN 2000178846 MEDLINE
DN 20178846 PubMed ID: 10716102
TI Rapid opiate detoxication in outpatient **treatment**: relationship with naltrexone compliance.
AU Gerra G; Zaimovic A; Rustichelli P; Fontanesi B; Zambelli U; Timpano M; Bocchi C; Delsignore R
CS Centro Studi Farmacotossicodipendenze-Servizio Tossicodipendenze, Az. USL di Parma, Italy.
SO JOURNAL OF SUBSTANCE ABUSE TREATMENT, (2000 Mar) 18 (2) 185-91.
Journal code: 8500909. ISSN: 0740-5472.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals
EM 200004
ED Entered STN: 20000427
Last Updated on STN: 20000427
Entered Medline: 20000419
AB A variety of detoxification methods have been utilized for the **treatment** of heroin withdrawal before individuals begin long-term opiate-free and naltrexone programs. While methadone in decreasing doses is still widely used for detoxication procedures, rapid and ultrarapid protocols including clonidine and opiate receptors antagonists have been proposed. This study compares the efficacy of different detoxification methods and investigates possible changes in naltrexone compliance. Ninety-eight heroin-addicted individuals were studied to evaluate withdrawal symptoms, craving, mood, urine toxicologic screens, and drop-out rate during therapy with: Group A: clonidine only (5 days); Group B: clonidine, oxazepam, baclofen, and ketoprofene with naloxone and naltrexone (2 days); and Group C: methadone in decreasing doses (10 days). Naltrexone compliance and relapse rates were evaluated during a 6-month follow-up period. Rapid detoxification with opiate antagonists (Group B) induced slight and transient withdrawal symptoms, and resulted in a

significantly lower percentage of heroin catabolites in urine controls during the detoxification procedure, lower negative and positive craving, less mood problems, and higher compliance in extended naltrexone **treatment**. In comparison with clonidine only (Group A) and methadone (Group C), the early use of naltrexone during detoxification in combination with benzodiazepines and clonidine facilitated extended naltrexone acceptance and improved the recovery outcome in outpatients.

L7 ANSWER 35 OF 66 MEDLINE on STN
AN 2000057368 MEDLINE
DN 20057368 PubMed ID: 10591411
TI Honokiol and magnolol increase the number of [3H] muscimol binding sites three-fold in rat forebrain membranes in vitro using a filtration assay, by allosterically increasing the affinities of low-affinity sites.
AU Squires R F; Ai J; Witt M R; Kahnberg P; Saederup E; Sterner O; Nielsen M
CS Center for Neurochemistry, The Nathan Kline Institute for Psychiatric Research Orangeburg, NY 10962, USA.. lajtha@nki.rfmh.org
SO NEUROCHEMICAL RESEARCH, (1999 Dec) 24 (12) 1593-602.
Journal code: 7613461. ISSN: 0364-3190.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200001
ED Entered STN: 20000124
Last Updated on STN: 20000124
Entered Medline: 20000110
AB 1. The bark of the root and stem of various Magnolia species has been used in Traditional Chinese Medicine to **treat** a variety of disorders including anxiety and nervous disturbances. The biphenolic compounds honokiol (H) and magnolol (M), the main components of the Chinese medicinal plant Magnolia officinalis, interact with **GABA** (A) receptors in rat brain in vitro. We compared the effects of H and M on [3H]muscimol (MUS) and [3H]flunitrazepam (FNM) binding using EDTA/water dialyzed rat brain membranes in a buffer containing 150 mM NaCl plus 5 mM Tris-HCl, pH 7.5 as well as [35S]t-butylbicyclophosphorothionate (TBPS) in 200 mM KBr plus 5 mM Tris-HCl, pH 7.5. H and M had similar enhancing effects on [3H]MUS as well as on [3H]FNM binding to rat brain membrane preparations, but H was 2.5 to 5.2 times more potent than M. 2. [3H]FNM binding. **GABA** alone almost doubled [3H]FNM binding with EC50 = 450 nM and 200 nM using forebrain and cerebellar membranes, respectively. In the presence of 5 microM H or M the EC50 values for **GABA** were decreased to 79 and 89 nM, respectively, using forebrain, and 39 and 78 nM, using cerebellar membranes. H and M potently enhanced the potentiating effect of 200 nM **GABA** on [3H]FNM binding with EC50 values of 0.61 microM and 1.6 microM using forebrain membranes, with maximal enhancements of 33 and 47%, respectively. Using cerebellar membranes, the corresponding values were 0.25 and 1.1 microM, and 22 and 34%. 3. [3H]MUS binding. H and M increased [3H]MUS binding to whole forebrain membranes about 3-fold with EC50 values of 6.0 and 15 microM. Using cerebellar membranes, H and M increased [3H]MUS binding approximately 68% with EC50 values of 2.3 and 12 microM, respectively. Scatchard analysis revealed that the enhancements of [3H]MUS binding were due primarily to increases in the number of binding sites (Bmax values) with no effect on the high affinity binding constants (Kd values). The enhancing effect of H and M were not additive. 4. [35S]TBPS binding. H and M displaced [35S]TBPS binding from sites on whole rat forebrain membranes with IC50 values of 7.8 and 6.0 microM, respectively. Using cerebellar membranes, the corresponding IC50 values were 5.3 and 4.8 microM. These inhibitory effects were reversed by the potent **GABA** (A) receptor blocker R5135 (10 nM), suggesting that H and M allosterically increase the affinity of **GABA**(A) receptors for **GABA** and MUS by binding to sites in **GABA**(A) receptor complexes. 5. Two monophenols, the anesthetic propofol (2,6-diisopropylphenol, P) and the anti-**inflammatory** diflunisal (2',4'-difluoro-4-hydroxy-3-biphenyl carboxylic acid, D) also enhanced [3H]MUS binding, decreased the EC50 values for **GABA** in enhancing [3H]FNM binding and potentiated the enhancing effect of 200 nM **GABA** on [3H]FNM binding, although enhancements of [3H]MUS binding for these monophenols

were smaller than those for H and M, using forebrain and cerebellar membranes. The enhancing effect of P and D on [3H]MUS binding were almost completely additive. 2,2'-biphenol was inactive on [3H]MUS and [3H]FNM binding. These, and other preliminary experiments, suggest that appropriate ortho (C2) and para (C4) substitution increases the **GABA**-potentiating activity of phenols. 6. The potentiation of GABAergic neurotransmission by H and M is probably involved in their previously reported anxiolytic and central depressant effects.

L7 ANSWER 36 OF 66 MEDLINE on STN
AN 2000029836 MEDLINE
DN 20029836 PubMed ID: 10561395
TI Effects of **GABA** receptor antagonist on trigeminal caudalis nociceptive neurons in normal and neonatally capsaicin-**treated** rats.
AU Chiang C Y; Kwan C L; Hu J W; Sessle B J
CS Faculty of Dentistry, University of Toronto, Toronto, Ontario M5G 1G6, Canada.
NC DE04786-(NIDCR)
SO JOURNAL OF NEUROPHYSIOLOGY, (1999 Nov) 82 (5) 2154-62.
Journal code: 0375404. ISSN: 0022-3077.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199912
ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991217
AB We have recently demonstrated that significant increases in cutaneous mechanoreceptive field (RF) size and spontaneous activity occur in nociceptive neurons of trigeminal subnucleus caudalis (Vc, the medullary dorsal horn) of adult rats depleted of C-fiber afferents by neonatal **treatment** with capsaicin. These neuronal changes in capsaicin-**treated** (CAP) rats are suggestive of central neuroplasticity and involve N-methyl-D-aspartic acid (NMDA) receptor mechanisms. The present study examined whether the **GABA**(A) receptor antagonist bicuculline (BIC) or the **GABA**(B) receptor antagonist 2-hydroxysaclofen (SAC) can influence the RF properties and activity of Vc nociceptive neurons classified as either nociceptive-specific or wide-dynamic range in CAP adult rats or in neonatally vehicle-**treated** (CON) rats. C-fiber depletion was confirmed in the CAP rats by a significant decrease in plasma extravasation of Evans blue dye in a skin area receiving topical application of mustard oil, a small-fiber excitant and **inflammatory** irritant. As previously reported, marked increases in cutaneous RF size and spontaneous activity occurred in Vc nociceptive neurons of adult CAP rats, compared with CON rats. **GABA**(A) receptor blockade by BIC (i.t.) in CON rats produced a significant increase in spontaneous activity and in pinch RF size and tactile RF size (or appearance of a tactile area in the RF of nociceptive-specific neurons), as well as a significant lowering of the mechanical threshold and a significant enhancement of responses to pinch stimuli applied to the RF. In CAP rats, **GABA**(A) receptor blockade also produced significant changes similar to those documented in CON rats, except for a paradoxical and significant decrease in pinch RF size and no noticeable changes in responses to pinch stimuli. **GABA**(B) receptor blockade by SAC (i.t.) did not produce any significant changes in Vc nociceptive neurons in either CON or CAP rats. These results suggest that **GABA**(A) receptor-mediated inhibition may be involved in maintaining the functional expression of Vc nociceptive neuronal properties in normal conditions, and that in animals depleted of their C-fiber afferents, some features of this **GABA**(A) receptor-mediated modulation may be disrupted such that a **GABA** (A) receptor-mediated excitation is manifested.

L7 ANSWER 37 OF 66 MEDLINE on STN
AN 1999297480 MEDLINE
DN 99297480 PubMed ID: 10371070
TI Peripheral **inflammation** is associated with decreased

veratridine-induced release of **GABA** in the rat ventrocaudal periaqueductal gray: microdialysis study.
AU Renno W M; Beitz A J
CS Department of Anatomy, King Saud University, College of Medicine, Abha Branch, Saudi Arabia.. a03a002@ksu.eda.sa
NC DA 06687 (NIDA)
DE 06682 (NIDCR)
NS 28016 (NINDS)
SO JOURNAL OF THE NEUROLOGICAL SCIENCES, (1999 Mar 1) 163 (2) 105-10.
Journal code: 0375403. ISSN: 0022-510X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199907
ED Entered STN: 19990806
Last Updated on STN: 20000303
Entered Medline: 19990723
AB Systemic administration of opiates or direct injection of opioid peptides into the periaqueductal gray (PAG) produces a profound antinociception which is thought to be associated with inhibition of neuronal activity in the PAG. This inhibitory effect has been postulated to result from opiate inhibition of GABAergic neurons in the PAG. Whether this opioid-GABAergic system is affected in acute pain state has not been investigated. The present study was thus designed to determine the effects of unilateral peripheral **inflammation** on ventrocaudal PAG gamma-aminobutyric acid (**GABA**) release in the rat using in vivo microdialysis and subsequent high pressure liquid chromatography (HPLC) analysis. Microdialysis was chosen to perform direct and dynamic studies of amino acid concentrations in the PAG in control rats and in animals subjected to acute and prolonged **inflammation** caused by injection of 120 microl of Complete Freund's Adjuvant (CFA) into the hind paw. **GABA** release was significantly decreased in the CFA **treated** groups both 24 h as well as 7 days post-**treatment** . **GABA** release decreased to approximately one-fourth that of the 24 h mineral oil control group. Likewise, veratridine-induced release of **GABA** was decreased in rats **treated** with CFA 7 days prior to dialysis. Systemic injection of naloxone (5 mg/kg i.p.) caused selective and significant block in the decrease of veratridine-induced release of **GABA** in the 24 h CFA-**treated** rats. Taken together with data from our previous studies, these results suggest that the decrease in veratridine-induced **GABA** release in this study may be due to an increase opiate inhibition of **GABA** resulting from the induction of acute or prolonged elevation of nociceptive input.

L7 ANSWER 38 OF 66 MEDLINE on STN
AN 1999194104 MEDLINE
DN 99194104 PubMed ID: 10096440
TI Morphine tolerance in arthritic rats and serotonergic system.
AU Li J Y; Wong C H; Huang K S; Liang K W; Lin M Y; Tan P P; Chen J C
CS Department of Anesthesiology, Chung-Gung Memorial Hospital, Tao-Yuan, Taiwan, ROC.
SO LIFE SCIENCES, (1999) 64 (10) PL111-6.
Journal code: 0375521. ISSN: 0024-3205.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199904
ED Entered STN: 19990426
Last Updated on STN: 19990426
Entered Medline: 19990413
AB To understand whether chronic **inflammation** alters the development of morphine tolerance, the tail-flick test was used to evaluate the analgesic effect of morphine (75 mg tablet, s.c.) in the arthritic rats at the day 9-12 after the inoculation with Freund's adjuvant. Spinal cord monoamines and amino acid neurotransmitters were concomitantly measured. Chronic **inflammation** attenuated the antinociceptive effect of morphine as tolerance developed faster in the

arthritic rats compared to the vehicle-**treated** controls. In addition, ratio of 5-hydroxyindole-3-acetic acid/5-hydroxytryptamine (5-HIAA/5-HT) increased in the lumbar spinal cord of arthritic rats without any change in the concentrations of norepinephrine, glutamate, aspartate or **GABA**. Interestingly, increased serotonin turnover in the spinal cord was observed in both control and arthritic rats 24 hours after morphine **treatment**. Overall, the results suggest a significant role of serotonin up-regulation in the spinal cord during chronic pain and the development of morphine tolerance.

L7 ANSWER 39 OF 66 MEDLINE on STN
AN 1998371215 MEDLINE
DN 98371215 PubMed ID: 9705576
TI Role of glucocorticoids in the modulation of corticotropin-releasing hormone mRNA level by the endogenous benzodiazepine receptor ligand octadecaneuropeptide in rat brain.
AU Givalois L; Li S; Pelletier G
CS Molecular Endocrinology Laboratory, CHUL Research Center of Laval University, Quebec, Canada.. LGivalois@univ-montp2.fr
SO NEUROENDOCRINOLOGY, (1998 Aug) 68 (2) 98-104.
Journal code: 0035665. ISSN: 0028-3835.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199809
ED Entered STN: 19981006
Last Updated on STN: 19981006
Entered Medline: 19980924
AB We have recently demonstrated that the endozepine octadecaneuropeptide (ODN) exerts an inhibitory influence on corticotropin-releasing hormone (CRH) mRNA expression. The effect is mediated by GABAA receptors and is reversed by adrenalectomy. In order to investigate the involvement of peripheral steroids and more particularly of glucocorticoids in the ODN modulation of CRH mRNA expression, we have evaluated, in adrenalectomized and castrated male rats (ADX/CX), the effect of dexamethasone (DEX) pretreatment on CRH mRNA expression induced by central injection of ODN. Variations in the CRH mRNA expression in the hypothalamic paraventricular nucleus have been studied using quantitative in situ hybridization. The intracerebroventricular injection of ODN (4 microg/kg), as previously reported, induced a significant inhibition of CRH mRNA expression in sham-operated rats (-33%). This inhibition was reversed in ADX/CX male rats (+65% vs. sham vehicle-injected rats and +20% vs. ADX/CX vehicle-injected rats). Pretreatment with DEX (5 mg/kg) during 4 days induced in ADX/CX rats a decrease of 22% (vs. ADX/CX vehicle-injected rats) in the CRH mRNA signal, which became comparable to that observed in sham vehicle-injected rats. Pretreatment of ADX/CX animals with DEX prevented the ODN-induced increase in CRH mRNA expression, inducing rather a 16 and 30% inhibition when compared to vehicle- and ODN-injected ADX/CX rats, respectively. Moreover the CRH mRNA levels observed in ODN-injected ADC/CX rats were higher than those observed in sham vehicle- and sham ODN-injected rats (+16% vs. sham vehicle-injected rats and +63% vs. sham ODN-injected rats). These results indicate that dexamethasone **treatment** in ADX/CX rats can restore mRNA levels to those observed in sham-operated animals but not the inhibiting effect induced by ODN. Together with previous findings, these results suggest that adrenal and/or gonadal factor(s) other than glucocorticoids are involved in ODN modulation of the HPA axis.

L7 ANSWER 40 OF 66 MEDLINE on STN
AN 1998260313 MEDLINE
DN 98260313 PubMed ID: 9580594
TI S-(+)-3-isobutylgaba and its stereoisomer reduces the amount of **inflammation** and hyperalgesia in an acute arthritis model in the rat.
AU Houghton A K; Lu Y; Westlund K N
CS Department of Anatomy and Neurosciences, University of Texas Medical Branch, Galveston, USA.
NC NS 32778 (NINDS)

SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1998 May) 285 (2) 533-8.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199806
ED Entered STN: 19980618
Last Updated on STN: 19980618
Entered Medline: 19980608
AB The present study investigated whether spinal administration of S-(+)-3-isobutylgaba (S-(+)-3-IBG) or its stereoisomer, R-(-)-3-isobutylgaba (R-(-)-3-IBG), are effective in reducing the hyperalgesia and swelling observed after injection of kaolin and carrageenan into the knee joint of the rat. The effects of pretreatment and post-**treatment** of S-(+)-3-IBG, R-(-)-3-IBG and artificial cerebrospinal fluid (aCSF) on the swelling, pain-related behavior scores and the heat hyperalgesia induced by knee joint **inflammation** were compared. Infusion of either S-(+)-3-IBG or R-(-)-3-IBG through a microdialysis fiber, implanted in the dorsal horn of the spinal cord, for 1.5 h before injection of kaolin and carrageenan resulted in a 20 to 30% reduction in joint swelling compared with aCSF-**treated** controls, and prevented the development of heat hyperalgesia and spontaneous pain. In contrast, infusion of either stereoisomer after the development of **inflammation** reduced the hyperalgesia but did not reduce the amount of joint swelling compared with aCSF-**treated** animals. In summary, S-(+)-3-IBG and R-(-)-3-IBG are effective antihyperalgesic agents when administered both before and after joint **inflammation**. In addition, if administered before injection of kaolin and carrageenan into the knee joint this drug can attenuate joint **inflammation**. Both the antihyperalgesic and anti-**inflammatory** properties of this drug probably are mediated through a central neurogenic mechanism.

L7 ANSWER 41 OF 66 MEDLINE on STN
AN 1998127008 MEDLINE
DN 98127008 PubMed ID: 9465860
TI Susac syndrome.
AU Papo T; Biousse V; Lehoang P; Fardeau C; N'Guyen N; Huong D L; Aumaitre O; Bousser M G; Godeau P; Piette J C
CS Department of Internal Medicine, Hopital Pitie-Salpetriere, Paris, France.
SO MEDICINE, (1998 Jan) 77 (1) 3-11. Ref: 33
Journal code: 2985248R. ISSN: 0025-7974.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW OF REPORTED CASES)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199803
ED Entered STN: 19980319
Last Updated on STN: 19980319
Entered Medline: 19980310
AB Susac syndrome is an occlusive arteriolar disease that provokes infarcts in the cochlea, retina, and brain of young subjects, mostly women. Its cause is unknown. Some infarcts may be asymptomatic and only revealed by ancillary investigation: 1) audiogram that shows bilateral sensorineural hearing loss predominating on low frequencies, 2) funduscopy and fluorescein retinal angiography demonstrating bilateral distal branch retinal artery occlusions, and 3) brain MRI T2-weighted images disclosing small multifocal hyperintensities in white and gray matter. **Treatment** options are not codified, ranging from antithrombotic drugs to immunomodulatory therapy. Course is self-limited after an active fluctuating phase. Dementia, blindness, and deafness are rare late sequelae, and half of patients return to normal life.

L7 ANSWER 42 OF 66 MEDLINE on STN
AN 1998054960 MEDLINE
DN 98054960 PubMed ID: 9393250

TI Therapeutic modification of nuclear factor kappa B binding activity and tumor necrosis factor-alpha gene expression during acute biliary pancreatitis.
AU Dunn J A; Li C; Ha T; Kao R L; Browder W
CS Department of Surgery, East Tennessee State University, Johnson City 37614, USA.
SO AMERICAN SURGEON, (1997 Dec) 63 (12) 1036-43; discussion 1043-4.
Journal code: 0370522. ISSN: 0003-1348.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199712
ED Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971216
AB The role of cytokines has been well documented in the pathogenesis of acute pancreatitis. Antibodies against specific cytokines have been used to **treat** pancreatitis, with mixed results. The transcription factor nuclear factor (NF)-kappa B is a pleiotropic regulator of many genes involved in stress and **inflammatory** responses. The aim of this study was to prevent the NF-kappa B binding activity and tumor necrosis factor (TNF)-alpha gene overexpression as a possible therapeutic intervention for acute pancreatitis. Reversible acute biliary pancreatitis was induced in male Sprague Dawley rats as established in this laboratory. The animals were sacrificed at 0, 5, 15, 30 min and 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours after the induction of pancreatitis. NF-kappa B binding activity was determined by electrophoretic mobility shift assay, and TNF-alpha gene expression was assayed by reverse transcription-PCR. NF-kappa B binding activity was markedly higher around 4 hours and persisted up to 24 hours after pancreatitis induction in animals with acute pancreatitis, whereas TNF-alpha mRNA levels peaked at 24 hours. When amobarbital (to block NF-kappa B activation) was given (60 mg/kg body weight, I.P.) 3 hours before induction of pancreatitis, the activation of NF-kappa B and the overexpression of TNF-alpha gene was prevented, with significantly decreased severity of pancreatitis as assessed by amylase and clinical recovery. We conclude that 1) preventing the activation of NF-kappa B eliminates the induced overexpression of **inflammatory** cytokines (TNF-alpha) in acute pancreatitis, 2) such intervention correlates with clinical improvement in pancreatitis, and 3) this genetic modification offers a possible therapeutic intervention in acute pancreatitis.

L7 ANSWER 43 OF 66 MEDLINE on STN
AN 97450307 MEDLINE
DN 97450307 PubMed ID: 9305295
TI Diagnosis, prophylaxis, and **treatment** of headaches in the athlete.
AU Swain R A; Kaplan B
CS Department of Family Medicine, School of Pharmacy, West Virginia University, Charleston, USA.
SO SOUTHERN MEDICAL JOURNAL, (1997 Sep) 90 (9) 878-88. Ref: 52
Journal code: 0404522. ISSN: 0038-4348.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199710
ED Entered STN: 19971024
Last Updated on STN: 19971024
Entered Medline: 19971016
AB BACKGROUND: Headaches are a common entity in the ambulatory population. Physicians involved in sports medicine must be able to accurately diagnose headaches in athletes and whether they are exacerbated by exertion. Many medications have proven or theoretical negative effects on athletic performance. Thus, we should consider all aspects of medical management and determine which therapy is least intrusive to the athlete's

performance. We planned this review because of the small number of papers available on the effects of various medications on athletic performance. METHODS: We used MEDLINE to search from 1992 to current citations, using the medical subject headings of headache, prophylaxis, **treatment**, review, athletes, and exercise, alone or in combination. RESULTS: Fifty-two articles were identified and deemed appropriate for inclusion in this review. CONCLUSIONS: Acute therapy for tension headaches in the athletic population is best done with nonsteroidal anti-**inflammatory** drugs. Prophylaxis of chronic, recurrent tension headaches is best accomplished by night-time tricyclic antidepressants (especially nortriptyline) or selective serotonin reuptake inhibitors. Acute therapy for athletes with migraines is best managed with sumatriptan or DHE 45 and prophylaxis can be accomplished with verapamil, antidepressants, or valproate. Exertional, cluster, and structural/infectious headaches are also discussed briefly.

L7 ANSWER 44 OF 66 MEDLINE on STN
AN 97418908 MEDLINE
DN 97418908 PubMed ID: 9274984
TI Dexamethasone, but not stress, induce measurable changes of mitochondrial benzodiazepine receptor mRNA levels in rats.
AU Siripurkpong P; Harnyuttanakorn P; Chindaduangratana C; Kotchabhakdi N; Wichyanuwat P; Casalotti S O
CS Neuro-Behavioural Biology Center, Institute of Science and Technology for Research and Development, Mahidol University, Nakorn Pathom, Thailand.
SO EUROPEAN JOURNAL OF PHARMACOLOGY, (1997 Jul 23) 331 (2-3) 227-35.
Journal code: 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199710
ED Entered STN: 19971224
Last Updated on STN: 19990129
Entered Medline: 19971027
AB The expression of the mitochondrial benzodiazepine receptor gene was assayed by a semi-quantitative non-radioactive reverse transcriptase polymerase chain reaction (RT-PCR) assay. The level of amplified mitochondrial benzodiazepine receptor mRNA was expressed as a ratio of either glyceraldehyde-3-phosphate dehydrogenase (GAPDH) or beta-actin mRNA co-amplified in the same RT-PCR assay. The relative amounts of mitochondrial benzodiazepine receptor RNA in several rat tissues were found to be similar to the previously reported relative amount of mitochondrial benzodiazepine receptor binding sites. The level of these binding sites has also been reported to be altered by stress stimuli. In this study we specifically measured the effect of stress on the mRNA levels of the mitochondrial benzodiazepine receptor as an alternative method to the binding assay in an attempt to understand the mechanism by which stress alters binding. Sprague-Dawley male rats were either forced to swim for 15 min in 18 degrees C water or restrained in a plastic cylinder for 45 min either once, or twice daily for 7 days. Neither the swim stress, nor acute or chronic restraint stress, caused a measurable statistically significant relative change in mitochondrial benzodiazepine receptor mRNA in the adrenal gland, kidney, testis and olfactory bulb. However, daily **treatment** of rats for 7 days with 4 mg/kg of dexamethasone caused a significant decrease in mitochondrial benzodiazepine receptor gene expression in adrenal glands. This finding and the measurement of the relative levels of mitochondrial benzodiazepine receptor mRNA in the various tissues indicate that mitochondrial benzodiazepine receptor density is regulated to some extent at the gene expression level. However, the lack of detectable stress-induced changes in mRNA levels for this receptor seem to indicate that either mRNA changes were below detectable levels or that other mechanisms may be involved in the previously reported stress-induced changes of mitochondrial benzodiazepine receptor density. Because the focus of this work was on the regulation of mitochondrial benzodiazepine receptor gene expression, ligand binding studies to determine changes in receptor densities were not performed.

L7 ANSWER 45 OF 66 MEDLINE on STN
AN 97413440 MEDLINE
DN 97413440 PubMed ID: 9269855
TI The GABAergic system of the dentate gyrus after withdrawal from chronic alcohol consumption: effects of intracerebral grafting and putative neuroprotective agents.
AU Cadete-Leite A; Brandao F; Andrade J P; Ribeiro-da-Silva A; Paula-Barbosa M M
CS Department of Anatomy, Porto Medical School, Portugal.
SO ALCOHOL AND ALCOHOLISM, (1997 Jul-Aug) 32 (4) 471-84.
Journal code: 8310684. ISSN: 0735-0414.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199710
ED Entered STN: 19971021
Last Updated on STN: 19980206
Entered Medline: 19971003
AB We have demonstrated that, in the rat hippocampal formation, withdrawal from chronic alcohol consumption aggravates the ethanol-induced loss of pyramidal neurons and dentate granule cells. We have also shown that intracerebral grafting and piracetam could have a protective effect in these conditions. In this study we utilized immunocytochemical methods to investigate whether gamma-aminobutyric acid (**GABA**)ergic dentate gyrus cells, which are known to be inhibitory, were also affected by withdrawal from alcohol and, if so, whether putative neuroprotective agents could ameliorate the alterations found. Rats were alcohol-fed for 6 months and further divided into several groups: (1) alcohol-fed for an extra 6 months; (2) withdrawn from alcohol for 6 months; (3) withdrawn and grafted with newborn rat hippocampal tissue; (4) withdrawn and orally **treated** with piracetam for 6 months; (5) withdrawn and **treated** systemically with monosialoganglioside GM1 for 6 months; (6) withdrawn and **treated** with the vehicle used to dissolve the GM1. Control animals were pair-fed. All animals were killed 12 months after the beginning of the experiment and processed for **GABA** immunocytochemistry. **GABA**-immunoreactive (IR) neurons in the dentate gyrus were quantified and we found that alcohol-fed animals had a significant reduction in the numerical profile density of **GABA** -IR neurons in the dentate gyrus as a whole and in the hilus and in the granular layer of the suprapyramidal limb. Withdrawal from alcohol aggravated the GABAergic neuronal loss. Of the **treatments** used, only piracetam had a striking beneficial effect. Data gathered from the present work and from our previous studies indicate that the neuronal loss following chronic alcohol consumption and withdrawal affects both excitatory and inhibitory neurons in the dentate gyrus and that piracetam may have a useful protective role in this condition.

L7 ANSWER 46 OF 66 MEDLINE on STN
AN 97340047 MEDLINE
DN 97340047 PubMed ID: 9196557
TI Effects of high doses of diazepam on carrageenin-induced paw edema in rats.
AU Lazzarini R; Paulino C A; Malucelli B E; Palermo-Neto J
CS Departamento de Patologia, Faculdade de Medicina Veterinaria e Zootecnia, Universidade de Sao Paulo, Brasil.
SO BRAZILIAN JOURNAL OF MEDICAL AND BIOLOGICAL RESEARCH, (1996 Nov) 29 (11) 1525-9.
Journal code: 8112917. ISSN: 0100-879X.
CY Brazil
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199709
ED Entered STN: 19970922
Last Updated on STN: 19970922
Entered Medline: 19970911
AB Benzodiazepine (BDZ) receptor sites play a relevant role in immune/ **inflammatory** reactions. Acute BDZ **treatments** were shown

not only to suppress cell proliferation in rat thymus but also to decrease TNF-alpha, IL-1 and IL-6 release from adult mouse macrophages. In the present investigation the effects of acute (10.0 and 20.0 mg/kg) and long-term (10.0 mg kg-1 day-1, for 21 days) diazepam **treatment** on carrageenin-induced paw edema were studied in rats. The results showed that acute **treatment** with high doses of diazepam decreased paw edema volume in a dose-dependent manner, and this effect was observed as early as 1 h after the administration of the 20.0 mg/kg dose and continued until the last measurement was performed (8 h). In contrast, long-term diazepam administration did not modify the phlogistic-induced edema. Taken together, these data show that 1) acute diazepam **treatment** with high doses decreases the volume of the acute **inflammatory** paw edema developed by the organism as a response to carrageenin-induced injury, and 2) long-term diazepam **treatment** induces tolerance to this effect. These results are discussed in the light of a possible effect of diazepam on the components of the rat cellular and humoral immune/**inflammatory** reaction such as T lymphocytes and/or interleukins.

L7 ANSWER 47 OF 66 MEDLINE on STN
AN 97283766 MEDLINE
DN 97283766 PubMed ID: 9137844
TI Possible mechanisms of valproate in migraine prophylaxis.
AU Cutrer F M; Limmroth V; Moskowitz M A
CS Department of Neurology, Massachusetts General Hospital, Charlestown 02129, USA.
NC K08 NS 01803 (NINDS)
SO CEPHALALGIA, (1997 Apr) 17 (2) 93-100. Ref: 84
Journal code: 8200710. ISSN: 0333-1024.
CY Norway
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199707
ED Entered STN: 19970805
Last Updated on STN: 19970805
Entered Medline: 19970718
AB Valproate has been shown to be an effective prophylactic **treatment** in migraine. Investigation of the mechanism of its antimigraine action is difficult due to the broad range of its biochemical effects and the complex nature of migraine pathophysiology. Valproate increases brain **GABA** levels and, in doing so, may suppress migraine-related events in the cortex, perivascular parasympathetics or trigeminal nucleus caudalis. There is experimental evidence that it suppresses neurogenic **inflammation** and directly attenuates nociceptive neurotransmission. In addition, valproate reportedly alters levels of excitatory and inhibitory neurotransmitters and exerts direct effects on neuronal membranes in vitro. Valproate's observed effect may ultimately result from a combination of actions at different loci.

L7 ANSWER 48 OF 66 MEDLINE on STN
AN 97166411 MEDLINE
DN 97166411 PubMed ID: 9014142
TI Evidence that a hybrid molecule of norfloxacin and biphenylacetic acid is a potent antagonist at the GABAA receptor.
AU Imanishi T; Akahane K; Akaike N
CS Department of Physiology, Kyushu University Faculty of Medicine, Fukuoka, Japan.
SO NEUROPHARMACOLOGY, (1996) 35 (9-10) 1271-7.
Journal code: 0236217. ISSN: 0028-3908.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199705
ED Entered STN: 19970523
Last Updated on STN: 19970523

Entered Medline: 19970512

AB The combination of some fluorinated quinolone antimicrobials and certain non-steroidal anti-**inflammatory** drugs (NSAIDs), such as fenbufen, has been reported to elicit serious convulsions in humans. Fluoroquinolones, including norfloxacin (NFLX) and NSAIDs synergistically inhibit GABAA receptors. The mechanism(s) of the synergism, however, at present remains unclear. In the present study, the hypothesis that NFLX and biphenylacetic acid (BPA), an active metabolite of fenbufen, undergo an intermolecular interaction to produce a more potent GABAA antagonist, was investigated by examining the effects of two hybrid molecules of NFLX linked with BPA on **GABA**-evoked whole cell currents, recorded from rat hippocampal neurons using the perforated-patch clamp technique. Hybrid-1, with a -CONH(CH2)3- chain between NFLX and BPA, inhibited the **GABA** response more potently than co-**treatment** with NFLX and BPA. In contrast, hybrid-2 with a -CONH- chain between NFLX and BPA, exhibited only a weak inhibition of the **GABA** response. The characterization of the inhibition of the **GABA** response in the presence of hybrid-1 was similar to that of the combination of NFLX and BPA regarding the following: (1) there was a rightward parallel shift of the concentration-response curve of **GABA** at lower concentrations and a suppression of the maximal response to **GABA** at higher concentrations; (2) it was voltage-independent; and (3) there was no influence on the reversal potential of the **GABA** response. These results therefore suggest that NFLX and BPA interact with the GABAA receptor at nearby sites and thus suppress the **GABA** response.

L7 ANSWER 49 OF 66 MEDLINE on STN
AN 97144924 MEDLINE
DN 97144924 PubMed ID: 8990596
TI Wolff Award 1996. The actions of valproate and neurosteroids in a model of trigeminal pain.
AU Cutrer F M; Moskowitz M A
CS Department of Neurology, Massachusetts General Hospital, Boston 02129, USA.
NC K08 NS 01803 (NINDS)
NS 21558 (NINDS)
SO HEADACHE, (1996 Nov-Dec) 36 (10) 579-85.
Journal code: 2985091R. ISSN: 0017-8748.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199702
ED Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970205

AB Gamma-aminobutyric acid (**GABA**) receptors are ubiquitous inhibitory receptors in the central and peripheral nervous systems. Valproic acid (2-propylpentanoic acid), which enhances **GABA** synthesis and blocks degradation, is useful in migraine **treatment** and may act through activation of **GABA** receptors to modulate trigeminal nociceptive neurons innervating the meninges. To investigate this possibility, we tested the effect of valproate and allopregnanolone, a metabolite of progesterone, which binds and modulates the **GABA** receptor in an animal model of cephalic pain. One hundred ten Hartley guinea pigs were pretreated with either valproate or allopregnanolone 30 minutes prior to activation of trigeminal afferent fibers via intracisternal injection of the irritant, capsaicin. The effects of valproic acid and allopregnanolone were examined on c-fos expression within the trigeminal nucleus caudalis (lamina I, II), the termination site for small unmyelinated C fibers projecting from the meninges. C-fos positive cells were counted at three representative levels (rostral, middle, and caudal) by an observer naive to the **treatment** group. We found that valproate (> or = 10 mg/kg, IP) reduced labeled cells by 52% ($P < 0.05$) and allopregnanolone (> or = 100 mg/kg, IP) reduced labeled cells by 42% ($P < 0.01$). Bicuculline (GABAA antagonist), but not phaclofen (GABAB antagonist), blocked the valproate effect, thereby documenting the importance of GABAA receptors. We conclude that the attenuation of c-fos-LI by valproate and allopregnanolone is mediated via

GABAA receptors. These studies complement prior experiments showing that valproic acid and allopregnanolone block neurogenic **inflammation** within the meninges via GABAA receptor-mediated mechanisms. The findings suggest a potential strategy for discovering new antimigraine drugs with high affinity for the GABAA receptor and its modulatory sites.

L7 ANSWER 50 OF 66 MEDLINE on STN
AN 97035203 MEDLINE
DN 97035203 PubMed ID: 8880859
TI Calcitonin gene-related peptide content, basal outflow and electrically-evoked release from monoarthritic rat spinal cord in vitro.
AU Malcangio M; Bowery N G
CS Department of Pharmacology, School of Pharmacy, London, UK.
SO PAIN, (1996 Aug) 66 (2-3) 351-8.
Journal code: 7508686. ISSN: 0304-3959.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199703
ED Entered STN: 19970313
Last Updated on STN: 19970313
Entered Medline: 19970306
AB In this study, Freund's adjuvant-induced monoarthritis in the rat hind paw was used to induce chronic pain and **inflammation**. In order to compare the basal outflow, electrically-evoked release and total content of calcitonin gene-related peptide like immunoreactivity (CGRP-LI) with previously reported changes in substance P (SP-LI), the lumbar enlargement of monoarthitic (complete Freund's adjuvant-**treated**, CFA rat) and control (incomplete Freund's adjuvant-**treated**, IFA rat) spinal cords were used. During the 4-wk period after injection, neither the basal nor the evoked release of CGRP-LI from CFA cords differed from controls. By contrast, we have previously reported that SP-LI release from CFA rat spinal cords was significantly higher than from controls, 21 days after inoculation with Freund's adjuvant. Electrically-evoked CGRP-LI release from 21-day CFA rat spinal cord slices was not modified by superfusion with a GABAB antagonist, CGP 36742 (100 microM) which could greatly increase SP-LI release. However, the release of both peptides was significantly increased to the same extent in IFA and normal tissue but to a lesser extent in CFA cords, by superfusion with the opioid antagonist naloxone (1 microM). In conclusion, CGRP-LI, unlike SP-LI, did not appear to be susceptible to any changes in the lumbar enlargement of the rat spinal cord during **inflammation** of the hind paw. In addition, CGRP-LI release was increased by antagonism of opiate but not GABAB receptors, suggesting that during chronic **inflammation** of one hind paw, the GABAB ergic system, unlike the opioid system, might be activated to selectively inhibit the enhanced SP-LI release but not CGRP-LI release which is not changed.

L7 ANSWER 51 OF 66 MEDLINE on STN
AN 96359849 MEDLINE
DN 96359849 PubMed ID: 8719796
TI Attenuation by valproate of c-fos immunoreactivity in trigeminal nucleus caudalis induced by intracisternal capsaicin.
AU Cutrer F M; Limmroth V; Ayata G; Moskowitz M A
CS Department of Neurology, Massachusetts General Hospital, Charlestown 02129, USA.
NC K08 NS 01803 (NINDS)
NS 21558 (NINDS)
SO BRITISH JOURNAL OF PHARMACOLOGY, (1995 Dec) 116 (8) 3199-204.
Journal code: 7502536. ISSN: 0007-1188.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199610
ED Entered STN: 19961022
Last Updated on STN: 19961022
Entered Medline: 19961010

AB 1. Valproic acid, useful in the **treatment** of migraine, is an inhibitor of gamma aminobutyric acid (**GABA**) aminotransferase and activator of glutamic acid decarboxylase. Its mechanism in migraine remains obscure. The effects of valproic acid (2-propylpentanoic acid) were examined on the number of cells expressing c-fos-like immunoreactivity (c-fos-LI), a marker of neuronal activation, within the trigeminal nucleus caudalis (lamina I, IIo, TNC) 2 h after intracisternal injection of the irritant, capsaicin (0.1 ml; 15.25 micrograms ml-1), in urethane-anaesthetized Hartley guinea-pigs. Positive cells were counted in eighteen sections (50 microns) at three representative levels (rostral, middle and caudal) within lamina I, IIo of the TNC in 90 animals. 2. Numerous cells were labelled after capsaicin instillation (244 +/- 25; 1 ml; 15.25 mM) but not after capsaicin vehicle (11 +/- 1). Positive cells were also found within the medial reticular nucleus, the area postrema and the nucleus of the solitary tract. A similar distribution has been demonstrated previously after application of intracisternal irritants such as autologous blood or carrageenin. 3. Valproate (> or = 10 mg kg-1, i.p.) reduced labelled cells by 52% ($P < 0.05$) in lamina I, IIo but not within the area postrema, the nucleus of the solitary tract or the medial reticular nucleus. A similar finding was obtained previously after administration of sumatriptan, dihydroergotamine or the NK1 receptor antagonist RPR 100,893. 4. Pretreatment with bicuculline (30 micrograms kg-1; i.p.), a GABAA antagonist, but not phaclofen (1 mg kg-1) a GABAB antagonist, reversed the effect of valproate and increased c-fos positive cells within lamina I, IIo. Somewhat paradoxically, bicuculline by itself (30 micrograms kg-1 i.p.) decreased the number of labelled cells suggesting that more than a single GABAergic mechanism can suppress c-fos expression. 5. We conclude that the mechanism of action of valproate is mediated via GABAA receptors. Since valproate decreases both c-fos expression and as previously shown, neurogenic **inflammation** within the meninges, the GABAA receptor complex might provide an important target for drug development in migraine and related headaches.

L7 ANSWER 52 OF 66 MEDLINE on STN
AN 95391915 MEDLINE
DN 95391915 PubMed ID: 7662908
TI Hyperfixation of 99mTc-HMPAO and hypofixation of 123I-iomazenil in acute herpes encephalitis.
AU Launes J; Hokkanen L; Nikkinen P; Liewendahl K; Salonen O; Siren J; Iivanainen M
CS Department of Neurology, University Central Hospital, Helsinki, Finland.
SO NEUROREPORT, (1995 May 30) 6 (8) 1203-6.
Journal code: 9100935. ISSN: 0959-4965.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199510
ED Entered STN: 19951020
Last Updated on STN: 19980206
Entered Medline: 19951010
AB We studied two patients with herpes encephalitis (HSE) by [99mTc]HMPAO and [123I]iomazenil single photon emission computed tomography. Increased uptake of HMPAO was seen for up to 63 days in the HSE affected brain area. Iomazenil binds to benzodiazepine receptors and can measure neurone loss. Decreased iomazenil uptake was observed a few days after onset, at a time when hyperfixation of HMPAO occurred. Because in HSE neurone loss occurs simultaneously with hyperfixation of HMPAO, it is unlikely that this hyperfixation is caused by increased neuronal activity, as in epilepsy. This suggests that the hyperfixation of HMPAO in HSE occurs in glia and is sustained by **inflammation**-related hypermetabolism and acidity. The early neurone loss in HSE stresses the importance of immediate antiviral **treatment**.

L7 ANSWER 53 OF 66 MEDLINE on STN
AN 95195983 MEDLINE
DN 95195983 PubMed ID: 7534191
TI Spinal cord SP release and hyperalgesia in monoarthritic rats: involvement of the GABAB receptor system.

AU Malcangio M; Bowery N G
CS Department of Pharmacology, School of Pharmacy, London.
SO BRITISH JOURNAL OF PHARMACOLOGY, (1994 Dec) 113 (4) 1561-6.
Journal code: 7502536. ISSN: 0007-1188.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199504
ED Entered STN: 19950427
Last Updated on STN: 19960129
Entered Medline: 19950419
AB 1. Monoarthritis was induced in Lewis rats by interdermal injection in the left hind paw of a suspension of Mycobacterium tubercolusis in mineral oil (500 micrograms 100 microliters-1). Controls were injected with 100 microliters mineral oil. 2. Withdrawal latencies to thermal stimuli of the **inflamed** paw, the contralateral and both paws of control rats were measured at daily intervals after injection by the plantar test. 3. After detection of the pain threshold, rat spinal cords were removed and horizontal dorsal slices were mounted in a 3-compartment bath to measure electrically-evoked release of substance P-like immunoreactivity (SP-LI). 4. The **inflamed** paw of monoarthritic rats exhibited a lower pain threshold to thermal stimuli than the contralateral paw of the same animals and both paws of control rats. **Inflamed** paw hyperalgesia was maximal two days after injection, and declined gradually between 7 to 21 days with no evidence of excitability of withdrawal reflexes after 28 days. 5. During the 28 days study, monoarthritic rats gained less weight than control rats. 6. Electrical stimulation of the dorsal roots attached to rat isolated spinal cord slices induced a significant increase (174 +/- 18% of basal outflow which was 30.3 fmol 8 ml-1, n = 5) in SP-LI release. 7. One-week after induction of **inflammation** no differences in the amount of SP-LI released from the spinal cord of incomplete Freund's adjuvant-**treated** rats (IFA) and Freund's adjuvant-**treated** rats (CFA) were detected.(ABSTRACT TRUNCATED AT 250 WORDS)

L7 ANSWER 54 OF 66 MEDLINE on STN
AN 95177972 MEDLINE
DN 95177972 PubMed ID: 7873092
TI Drug-induced taste and smell disorders. Incidence, mechanisms and management related primarily to **treatment** of sensory receptor dysfunction.
AU Henkin R I
CS Taste and Smell Clinic, Center for Molecular Nutrition and Sensory Disorders, Washington, DC 20016.
SO DRUG SAFETY, (1994 Nov) 11 (5) 318-77. Ref: 682
Journal code: 9002928. ISSN: 0114-5916.
CY New Zealand
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199504
ED Entered STN: 19950419
Last Updated on STN: 20000303
Entered Medline: 19950404
AB Drugs in every major pharmacological category can impair both taste and smell function and do so more commonly than presently appreciated. Impairment usually affects sensory function at a molecular level, causing 2 major behavioural changes--loss of acuity (i.e. hypogeusia and hyposmia) and/or distortion of function (i.e. dysgeusia and dysosmia). These changes can impair appetite, food intake, cause significant lifestyle changes and may require discontinuation of drug administration. Loss of acuity occurs primarily by drug inactivation of receptor function through inhibition of tastant/odorant receptor: (i) binding; (ii) Gs protein function; (iii) inositol trisphosphate function; (iv) channel (Ca++,Na++) activity; (v) other receptor inhibiting effects; or (vi) some combination of these effects. Distortions occur primarily by a drug inducing abnormal

persistence of receptor activity (i.e. normal receptor inactivation does not occur) or through failure to activate: (i) various receptor kinases; (ii) Gi protein function; (iii) cytochrome P450 enzymes; or other effects which usually (iv) turn off receptor function; (v) inactivate tastant/odorant receptor binding; or (vi) some combination of these effects. Termination of drug therapy is commonly associated with termination of taste/smell dysfunction, but occasionally effects persist and require specific therapy to alleviate symptoms. **Treatment** primarily requires restoration of normal sensory receptor growth, development and/or function. **Treatment** which restores sensory acuity requires correction of steps initiating receptor and other pathology and includes zinc, theophylline, magnesium and fluoride. **Treatment** which inhibits sensory distortions requires reactivation of biochemical inhibition at the receptor or inactivation of inappropriate stimulus receptor binding and/or correction of other steps initiating pathology including dopaminergic antagonists, gamma-aminobutyric acid (**GABA**)-ergic agonists, calcium channel blockers and some orally active local anaesthetic, antiarrhythmic drugs.

L7 ANSWER 55 OF 66 MEDLINE on STN
AN 95157170 MEDLINE
DN 95157170 PubMed ID: 7854044
TI Expression of GAD mRNA in spinal cord neurons of normal and monoarthritic rats.
AU Castro-Lopes J M; Tolle T R; Pan B; Zieglgansberger W
CS Institute of Histology and Embryology, Faculty of Medicine of Oporto, Porto, Portugal.
SO BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, (1994 Oct) 26 (1-2) 169-76. Journal code: 8908640. ISSN: 0169-328X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199503
ED Entered STN: 19950322
Last Updated on STN: 19950322
Entered Medline: 19950316
AB This study was carried out to investigate whether the increase of **GABA** levels in spinal cord dorsal horn in response to chronic **inflammatory** lesions results from an enhanced expression of the gene that governs the production of glutamate decarboxylase (GAD), the enzyme responsible for **GABA** synthesis. In situ hybridization was used to visualize neurons expressing GAD mRNA within the spinal cord, in both intact rats and in animals bearing chronic monoarthritis induced by intraarticular injection of complete Freund's adjuvant. In control normal animals, neuronal labeling by an antisense oligonucleotide probe occurred throughout the spinal gray matter, except in the motoneuronal pool of Rexed's lamina IX. In **treated** animals 4 days after the induction of monoarthritis, a significant increase in the number of labeled cells occurred in the superficial laminae (25.3%) and the neck (17.2%) of the ipsilateral dorsal horn at segments L4-L5 which contain the projection domain of the ankle joint. At 2 weeks, values were, respectively, 20.2% and 13.9% over contralateral values, and an increase of 12.4% was found in the ventral horn. At 3 weeks, the ipsilateral increase of labeled cells was restricted to the superficial dorsal horn (15.2%). These findings emphasize the role played by the spinal GABAergic system in the modulation of chronic nociceptive input. It is suggested that the response of the spinal GABAergic system depends on the activation of GAD gene transcription in spinal neurons.

L7 ANSWER 56 OF 66 MEDLINE on STN
AN 95082155 MEDLINE
DN 95082155 PubMed ID: 7990268
TI Involvement of pain associated anxiety in the development of morphine tolerance in formalin **treated** mice.
AU Rahman A F; Takahashi M; Kaneto H
CS Department of Pharmacology, Faculty of Pharmaceutical Sciences, Nagasaki University, Japan.
SO JAPANESE JOURNAL OF PHARMACOLOGY, (1994 Aug) 65 (4) 313-7.

Journal code: 2983305R. ISSN: 0021-5198.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199501
ED Entered STN: 19950124
Last Updated on STN: 19950124
Entered Medline: 19950106
AB The mechanism underlying the previous findings that the development of antinociceptive tolerance to morphine was significantly delayed in the presence of **inflammatory** pain induced by formalin was examined. Measurements of the pain threshold at different time intervals have shown that pain lasts around one week in the formalin **treated** mice. A single dose of indomethacin (10 mg/kg) or aspirin (400 mg/kg), 30 min before formalin injection, and daily 400 mg/kg of aspirin had no effects on the pain threshold or swelling, and it also did not affect the delay of morphine tolerance development. Daily administration of diazepam, 1 mg/kg, 1 hr before morphine injection completely abolished the delay. This effect was antagonized by 2 mg/kg of flumazenil, administered 15 min before diazepam injection. These results suggest that pain-associated anxiety participates in the delay of morphine tolerance development and consequently the benzodiazepine-receptor complex plays a role in the development of morphine tolerance during a painful state.

L7 ANSWER 57 OF 66 MEDLINE on STN
AN 95055132 MEDLINE
DN 95055132 PubMed ID: 7965759
TI **Inflammation**-induced release of excitatory amino acids is prevented by spinal administration of a GABAA but not by a GABAB receptor antagonist in rats.
AU Sluka K A; Willis W D; Westlund K N
CS Marine Biomedical Institute, University of Texas Medical Branch, Galveston.
NC NS01445 (NINDS)
NS11255 (NINDS)
NS28064 (NINDS)
+
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1994 Oct) 271 (1) 76-82.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199411
ED Entered STN: 19950110
Last Updated on STN: 19950110
Entered Medline: 19941125
AB After the injection of kaolin and carrageenan into the knee joint of rats, there was a decrease in paw withdrawal latency (PWL) to radiant heat ipsilaterally, which indicates hyperalgesia. This decrease was blocked by pretreatment of the spinal cord dorsal horn with the gamma-aminobutyric acid (GABAA) receptor antagonist, bicuculline but not with the GABAB receptor antagonist, CGP35348, administered by microdialysis. The **inflammation**-induced release of amino acids from the spinal dorsal horn occurred in two phases: 1) an early phase at the time of injection and 2) a late phase at 3.5 to 8 hr. The amino acids released in the late phase included aspartate (ASP), glutamate (GLU) and glutamine. During the PWL test, there was also the release of the inhibitory amino acids, serine and glycine, after the induction of arthritis. The increased release of excitatory amino acids at the time of injection was unaffected by pretreatment with either bicuculline or CGP35348. The release of amino acids during the late phase and during the PWL test was blocked by pretreatment with bicuculline but not CGP35348. The increase in joint circumference typical of this model did not occur with pretreatment with the GABAA receptor antagonist. The change in joint circumference was positively correlated with the late phase release of ASP and GLU. In bicuculline-**treated** arthritic animals in which joint

inflammation was minimal, concentrations of ASP and GLU did not increase above base line.

L7 ANSWER 58 OF 66 MEDLINE on STN
AN 94363973 MEDLINE
DN 94363973 PubMed ID: 8082355
TI Inhibition of bronchial hyperresponsiveness by the **GABA**-agonist baclofen.
AU Dicpinigaitis P V; Spungen A M; Bauman W A; Absgarten A; Almenoff P L
CS Department of Medicine, Mount Sinai School of Medicine, New York.
SO CHEST, (1994 Sep) 106 (3) 758-61.
Journal code: 0231335. ISSN: 0012-3692.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199410
ED Entered STN: 19941021
Last Updated on STN: 19990129
Entered Medline: 19941013
AB gamma-Aminobutyric acid (**GABA**) is a well-known inhibitory transmitter of the central nervous system. Recently, the presence of **GABA** and its receptors has been confirmed in peripheral tissues, including lung tissue. gamma-Aminobutyric acid and the **GABA** -agonist baclofen have been shown in animal studies to inhibit airway responsiveness to various bronchoconstricting agents. The results of these investigations suggest the possibility of a role for baclofen in the therapy of human airway hyperreactivity. We recently showed that subjects with cervical spinal cord injury (quadriplegia) uniformly exhibit hyperresponsiveness to methacholine. The interruption of sympathetic airway innervation and resultant unopposed cholinergic tone occurring after transection of the cervical spine are thought to explain this phenomenon. We compared bronchial responsiveness with methacholine (PC20) in a control group of otherwise healthy quadriplegic nonsmokers (n = 8) with a similar group of subjects (n = 6) maintained on baclofen for the relief of muscle spasm. Mean PC20 (mg/ml) among the control group was 1.42 +/- 1.6(SD) vs 15.0 +/- 9.1 in the baclofen group (p = 0.001). The inhibition of bronchial hyperresponsiveness in subjects with cervical spinal cord injury maintained on chronic baclofen therapy suggests the drug's ability to block neuronal acetylcholine release within airways, as well as a possible direct effect on airway smooth muscle. This action of baclofen, along with its documented ability in animal lung to inhibit release of other **inflammatory** mediators, supports further investigation of this drug as a potential therapeutic agent for asthma **treatment**.

L7 ANSWER 59 OF 66 MEDLINE on STN
AN 94277602 MEDLINE
DN 94277602 PubMed ID: 8008409
TI Carrageenan-induced **inflammation** of the hind foot provokes a rise of **GABA**-immunoreactive cells in the rat spinal cord that is prevented by peripheral neurectomy or neonatal capsaicin **treatment**.
AU Castro-Lopes J M; Tavares I; Tolle T R; Coimbra A
CS Institute of Histology and Embryology, Faculty of Medicine of Oporto, Porto, Portugal.
SO PAIN, (1994 Feb) 56 (2) 193-201.
Journal code: 7508686. ISSN: 0304-3959.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199407
ED Entered STN: 19940729
Last Updated on STN: 19940729
Entered Medline: 19940719
AB An increase in the number of gamma-aminobutyric acid (**GABA**)-immunoreactive cells is reported in the superficial dorsal horn of the rat spinal cord upon unilateral **inflammation** of the hind foot

caused by subcutaneous carrageenan injection. The rise of GABAergic cells was restricted to the ipsilateral dorsal horn, reaching a peak value of 23.4% over the contralateral side 4 days after carrageenan injection. Sciatic neurectomy or neonatal capsaicin **treatment** prevented this effect. These findings suggest that dorsal horn **GABA** is up-regulated by the increase of noxious inflow conveyed by unmyelinated C fibers from the **inflamed** tissues.

L7 ANSWER 60 OF 66 MEDLINE on STN
AN 93140711 MEDLINE
DN 93140711 PubMed ID: 8380885
TI Modulation of tumor necrosis factor-alpha, interleukin-1 beta, interleukin-6, interleukin-8, and granulocyte/macrophage colony-stimulating factor expression in human monocytes by an endogenous anxiogenic benzodiazepine ligand, triakontatetraneuropeptide: evidence for a role of prostaglandins.
AU Taupin V; Gogusev J; Descamps-Latscha B; Zavala F
CS INSERM U25, Hopital NECKER, Paris, France.
SO MOLECULAR PHARMACOLOGY, (1993 Jan) 43 (1) 64-9.
Journal code: 0035623. ISSN: 0026-895X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199302
ED Entered STN: 19930312
Last Updated on STN: 19930312
Entered Medline: 19930223
AB Triakontatetraneuropeptide (TTN) is the major processing product of the endogenous anxiogenic peptide ligand of the benzodiazepine receptor, diazepam binding inhibitor. In the present study, we demonstrated by Northern blot analysis that the mRNA levels for tumor necrosis factor-alpha (TNF-alpha), interleukin (IL)-1 beta, granulocyte/macrophage colony-stimulating factor, IL-6, and IL-8 were significantly increased after 4 hr of incubation of human monocytes with lipopolysaccharide (LPS) and TTN (10(-11) M), compared with cells incubated with LPS alone. Exposure of monocytes for 20 hr to LPS and TTN (10(-11) M) also stimulated TNF-alpha, IL-1 beta and granulocyte/macrophage colony-stimulating factor release by 80%, 110%, and 98%, respectively, relative to the response elicited by LPS alone. Smaller stimulatory effects were observed using the prototypic pharmacological peripheral benzodiazepine Ro5-4864 (10(-11) M) (55%, 72%, and 62%, assessed by means of specific enzyme immunoassays). In contrast, TTN and Ro5-4864 did not modulate LPS-induced IL-6 and IL-8 production. **Treatment** with the cyclooxygenase inhibitor indomethacin increased IL-1 beta and TNF-alpha secretion but not that of IL-6 or IL-8. The observed stimulatory effects of TTN and indomethacin were not additive. Taken together, these findings suggest a common mechanism of action for TTN and indomethacin, involving PG formation. In this respect, TTN inhibited prostaglandin (PG) E2 production by 30%. The fact that the observed modulatory effects correlated with PG levels suggests the existence of a second-messenger pathway associated with the peripheral-type benzodiazepine receptor. These results indicate that human TTN differentially modulates the LPS-induced expression of proinflammatory cytokines, and they further support the concept that this endogenous psychoactive peptide could be involved in physiological control of the **inflammatory** response.

L7 ANSWER 61 OF 66 MEDLINE on STN
AN 92217850 MEDLINE
DN 92217850 PubMed ID: 1313778
TI Effects of the combination of new quinolones and a nonsteroidal anti-**inflammatory** drug, fenbufen, on the EEG of rabbits.
AU Suzuki T; Hara Y; Tamagawa M; Kakizaki K; Murayama S
CS Department of Pharmacology, School of Medicine, Chiba University, Japan.
SO NIPPON YAKURIGAKU ZASSHI. FOLIA PHARMACOLOGICA JAPONICA, (1992 Jan) 99 (1) 45-54.
Journal code: 0420550. ISSN: 0015-5691.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)

LA Japanese
FS Priority Journals
EM 199205
ED Entered STN: 19920529
Last Updated on STN: 19920529
Entered Medline: 19920513
AB A combination of fenbufen, a non-steroidal anti-**inflammatory** drug and the new quinolone produces a central stimulating action. To confirm the action, we used 6 kinds of new quinolones: enoxacin, norfloxacin, ofloxacin, ciprofloxacin, lomefloxacin and tosufloxacin in this experiment. The convulsive effects of these drugs were tested on the EEG recorded from the neocortex and subcortical regions of the rabbits. Animals **treated** with fenbufen (50-200 mg/kg, p.o.) tended to have a high amplitude slow wave in their EEG. Rabbits **treated** with the new quinolones at the dose of 100 mg/kg, p.o., with the exception of tosufloxacin, also tended to show a high amplitude slow wave in their EEG. Each new quinolone given 30 min after fenbufen (50 mg/kg, p.o.) elicited characteristic spikes on the EEG. Then, high-frequency-spikes and epileptiform seizure waves appeared for a long experimental period with this combination. The combination of fenbufen and tosufloxacin (100-400 mg/kg, p.o.) caused no changes in EEG and behavior. The spike and epileptiform wave could be suppressed only temporarily with diazepam (1-4 mg/kg, i.v.). These results suggest that combined use of fenbufen and one of the new quinolones, except for tosufloxacin, produces the seizure. Not only **GABA** but also several other mechanisms in the central nervous system may be involved in the convulsion.

L7 ANSWER 62 OF 66 MEDLINE on STN
AN 92173986 MEDLINE
DN 92173986 PubMed ID: 1311618
TI Increased hypothalamic [3H]flunitrazepam binding in hypothalamic-pituitary-adrenal axis hyporesponsive Lewis rats.
AU Smith C C; Hauser E; Renaud N K; Leff A; Aksentijevich S; Chrousos G P; Wilder R L; Gold P W; Sternberg E M
CS Unit on Neuroendocrine Immunology and Behavior, NICHD, Bethesda, MD 20892.
SO BRAIN RESEARCH, (1992 Jan 13) 569 (2) 295-9.
Journal code: 0045503. ISSN: 0006-8993.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199204
ED Entered STN: 19920424
Last Updated on STN: 19970203
Entered Medline: 19920403
AB We have previously demonstrated that susceptibility of Lewis (LEW/N) rats to **inflammatory** disease, compared to relatively resistant Fischer (F344/N) rats, is related to deficient glucocorticoid counter-regulation of the immune response resulting from deficient corticotropin-releasing hormone (CRH) responsiveness to **inflammatory** and other stress mediators. The **GABA** /benzodiazepine receptor complex is an important negative modulator of CRH secretion and responsiveness to excitatory stimuli. In this study, we have examined in vitro binding of [3H]flunitrazepam to hypothalamic membrane preparations from LEW/N and F344/N rats. LEW/N rats had significantly more hypothalamic benzodiazepine binding sites (Bmax) than F344/N rats, but there were no differences in benzodiazepine binding affinities (Kd) between these two strains. The differences in benzodiazepine receptor number were consistent with the respective plasma corticosterone levels in the two strains, and with previous work indicating a negative correlation between corticosterone levels and benzodiazepine binding site number. Adrenalectomy of F344/N rats increased benzodiazepine binding to levels comparable to LEW/N animals and **treatment** of adrenalectomized F344/N rats with DEX resulted in lowering of benzodiazepine Bmax to levels that did not differ significantly from those of intact F344/N rats. There was no significant change in receptor number in either adrenalectomized or DEX-**treated** LEW/N rats. These findings suggest that basal benzodiazepine receptor differences between these strains may be partially

related to strain differences in corticosterone levels, however that additional factors may contribute to maintenance of these differences in LEW/N rats. Since benzodiazepines attenuate hypothalamic CRH secretion through GABAergic inhibition, we suggest that strain differences in receptor number could also augment strain differences in hypothalamic-pituitary-adrenal axis function through differential sensitivity to **GABA**-mediated feedback.

L7 ANSWER 63 OF 66 MEDLINE on STN
AN 91031362 MEDLINE
DN 91031362 PubMed ID: 2226373
TI Post-traumatic epilepsy: cellular mechanisms and implications for **treatment**.
AU Willmore L J
CS Department of Neurology, University of Texas Medical School, Houston 77030.
NC NS-16704 (NINDS)
SO EPILEPSIA, (1990) 31 Suppl 3 S67-73. Ref: 79
Journal code: 2983306R. ISSN: 0013-9580.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199012
ED Entered STN: 19910208
Last Updated on STN: 20000303
Entered Medline: 19901213
AB Epilepsy complicates severe head trauma. Development of persistent seizures appears to correlate with the extent of trauma. Although early reports suggested that prophylactic administration of antiepileptic drugs would prevent epileptogenesis, controlled studies have failed to corroborate this assumption. Head trauma initiates a sequence of responses that includes altered blood flow and vasoregulation, disruption of the blood-brain barrier, increases in intracranial pressure, focal or diffuse ischemia, hemorrhage, **inflammation**, necrosis, and disruption of fiber tracts. The presence of an intracranial hematoma has a robust association with the development of post-traumatic epilepsy. Extravasation of blood is followed by hemolysis and deposition of heme-containing compounds into the neuropil, initiating a sequence of univalent redox reactions and generating various free radical species, including superoxides, hydroxyl radicals, peroxides, and perferryl ions. Free radicals initiate peroxidation reactions by hydrogen abstraction from methylene groups adjacent to double bonds of fatty acids and lipids within cellular membranes. Intrinsic enzymatic mechanisms for control of free radical reactions include activation of catalase, peroxidase, and superoxide dismutase. Steroids, proteins, and tocopherol also terminate peroxidative reactions. Tocopherol and selenium are effective in preventing tissue injury initiated by ferrous chloride and heme compounds. **Treatment** strategies for prevention or prophylaxis of post-traumatic epilepsy must await absolute knowledge of mechanisms. Antioxidants and chelators may be useful, given the speculation that peroxidative reactions may be an important component of brain injury responses. However, potential **treatment** strategies involving gamma-aminobutyric acid (**GABA**) agonists, NMDA receptor antagonists, and barbiturates need further scientific assessment.

L7 ANSWER 64 OF 66 MEDLINE on STN
AN 89095326 MEDLINE
DN 89095326 PubMed ID: 3210443
TI Mechanism of the analgesic effect of neurotropin.
AU Hata T; Kita T; Itoh E; Oyama R; Kawabata A
CS Department of Pharmacology, Faculty of Pharmacy, Kinki University, Osaka, Japan.
SO JAPANESE JOURNAL OF PHARMACOLOGY, (1988 Oct) 48 (2) 165-73.
Journal code: 2983305R. ISSN: 0021-5198.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals
EM 198902
ED Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19890223
AB Neurotropin, an extract from the **inflamed** skin of vaccinia virus-inoculated rabbits, has been observed clinically to be effective for **treating** pain in patients with lumbago, SMON and other neuropathies. In the present study, we examined the mechanism of the antinociceptive effect of neurotropin in mice in relation to administration routes, opioids, and noradrenergic or GABAergic drugs, by the tail pressure method. The antinociceptive effects of neurotropin were large when administered by the i.p. and intracisternal (i.cist.) routes, but comparatively small in the case of the intrathecal (i.th.) route. Neurotropin may thus act at the supraspinal level rather than on the spinal cord. The antinociceptive effect of neurotropin was not blocked by naloxone, and no cross-tolerance developed between neurotropin and morphine. The effect of neurotropin was blocked by phentolamine and reserpine, but not by atropine. Its effect was enhanced by **GABA**, muscimol, aminooxyacetic acid and diaminobutyric acid, but not by baclofen, and blocked by bicuculline methiodide. From these results, the antinociceptive action of neurotropin appears to be non-opioid in nature, and may possible be mediated by the noradrenergic and GABAergic systems, but unrelated to the cholinergic system.

L7 ANSWER 65 OF 66 MEDLINE on STN
AN 88193771 MEDLINE
DN 88193771 PubMed ID: 2896040
TI Biochemical and histological modifications of the rat retina induced by the cholinergic neurotoxin AF64A.
AU Estrada C; Triguero D; Martin del Rio R; Gomez Ramos P
CS Dep. de Fisiologia, Facultad de Medicina, Universidad Autonoma de Madrid, Spain.
SO BRAIN RESEARCH, (1988 Jan 26) 439 (1-2) 107-15.
Journal code: 0045503. ISSN: 0006-8993.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198806
ED Entered STN: 19900308
Last Updated on STN: 19980206
Entered Medline: 19880608
AB Intraocular injections of ethylcholine mustard aziridinium ion (AF64A) in the rat depressed retinal choline acetyltransferase (ChAT) activity in a dose-dependent manner without any significant change in the content of amino acid neurotransmitters **GABA**, glycine, aspartate and glutamate. ChAT reduction was already detected 24 h after the injection and persisted for at least one month. In vitro AF64A also inhibited retinal ChAT activity. No changes in muscarinic receptor sites were detected. The histological study showed light cells, characterized by cytoplasmic swelling in the innermost part of the inner nuclear layer and in the ganglion cell layer. We suggest that these light cells are the cholinergic retinal neurons affected by the toxin. In addition, dark cells in the inner nuclear layer, large empty spaces in the outer nuclear layer, **inflammatory** infiltrate and vascular alterations were also observed in **treated** retinas. Choline uptake systems in photoreceptors and in endothelial cells or cholinergic perivascular nerve endings may explain the lesions observed in the outer nuclear layer and the vascular alterations.

L7 ANSWER 66 OF 66 MEDLINE on STN
AN 83014519 MEDLINE
DN 83014519 PubMed ID: 6181489
TI Prevention of damage in acute spinal cord injury by peptides and pharmacologic agents.
AU Naftchi N E
SO PEPTIDES, (1982 May-Jun) 3 (3) 235-47.

Journal code: 8008690. ISSN: 0196-9781.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198212
ED Entered STN: 19900317
Last Updated on STN: 19900317
Entered Medline: 19821202
AB Cats were used as models of traumatic spinal cord injury. Each experimental animal received a 500 g-cm force to the exposed dura at the level of thoracic fourth vertebra. Somatosensory evoked potentials (SEPs), carotid arterial blood pressure (BP), and abdominal aorta blood flow in the **treated** groups were compared with those of the control group. The three **treated** groups received naloxone (5 mg/kg), TRH (5 mg/kg), and a combination of methyl-prednisolone sodium succinate (MP, 35 mg/kg) and epsilon-aminocaproic acid (EACA, 350 mg/kg). The SEPs which were done only in the naloxone **treated** group approached "normalcy" 24-26 hours after trauma as compared with the absence of SEPs in traumatized untreated group. In all three groups, the **treatment** increased the blood flow in abdominal aorta significantly. Morphine sulfate increased substance P (SP) immunoreactivity in the dorsal and ventral gray matter. Naloxone not only reversed this effect, it depleted SP below the saline control level. In order to establish that lipid free radicals are responsible for damage to biological membranes, their effects were also investigated in vitro: 14C-**GABA** uptake by mouse cortical slices which had decreased by 33% in the presence of superoxide (. O-2) generating system, horseradish peroxidase (HRP), was reduced only by 9% when superoxide dismutase was added to the medium. The latter also protected the nerve endings from damage by (. O-2) as examined by electron microscopy. It is concluded that the agents used in this study produce their ameliorating effects by virtue of their anti-**inflammatory**, anti-oxidant, and membrane stabilizing properties in addition to their effect on enhancing the regional microcirculation. The release of SP by naloxone may be responsible for the increase in blood flow. The consequences of traumatic injury as depicted in Fig. 1 are discussed at length.

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